A CLINICAL EVALUATION OF CARDIOVASCULAR STABILITY AND RESPIRATORY CHANGES WITH NEUROLEPTANALGESIA

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CERTIFICATE

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CERTIFICATE

This is to certify that the work and technique described in this thesis entitled "A CLINICAL EVALUATION OF CARDIOVASCULAR STABILITY AND RESPIRATORY CHANGES WITH NEUROLEPTANALGESIA', have been under taken by Dr.(Mrs) VEENA GUPTA herself under our guidance and supervision and have been periodically checked by us.

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C O N T E N T S

INTRODUCTION

For more than a century it has commonly been accepted that general anaesthesia can safely protect an organism from surgical pain only if cortical and subcortical centres are effectively depressed. The effecacy of agents used to produce such an anaesthetic state has been judged according to how fast they could induce optimal cerebral depression, with minimum circulatory, respiratory and metabolic derangements and how readily their effects can be overcome.

Laborit (1959) first drew attention to the need for revising the old conventional approach to general anaesthesia by introducing a new concept on selective blocking of certain cellular, autonomic and endocrine mechanism normally activated as a response to stress. Drug combination capable of causing such multifocal inhibition were used to produce a state of rest in such structures as the cerebral cortex, the diencephalon, certain hormonal relays and various ganglionic and terminal synapses. Naturally this artificial hibernation was often marked by circulatory depression resulting from induced homeostatic imbalance.

The search for other means of selectively blocking the afferent system involved in surgical stress has led to increased emphasis on the possibility of combining analgesic agent with agents that suppress vegetative reflexes.

It is an old and steady effort of pharmacologists to produce such anaesthetic drugs of selective action, free from toxic effects and having minimum side effects, easy to control, which can widely be applied to anaesthesia in diagnostic and therapeutic interventions.

After Janssen (1962) introduced a series of highly potent analgesic and neuroleptic agents in 1958 an anaesthetic technique was evolved, called 'NEUROLEPTAN-ALGESIA'. This renders the patients free from pain without effecting certain areas of the central nervous system that are blocked in orthodox anaesthesia.

The term Neuroleptanalgesia was proposed by De-Castro and Mundeleer (1959) to describe a state of indifference and immobilization produced by combined administration of the neuroleptic drug Haloperidol and the narcotic analgesic Phenoperidine.

Neuroleptanalgesia is a method of general anaesthesia, differing significantly from the classical anaesthetic technique both in their mechanism and appearence. The function of cortex directing the perceptive and conscious activity, does not cease under the effect of the neuroleptic agent administered in combination but the patient would become completely insensible in relation to the events with and around him. The pain sensation together with its reflex

consequences stops under the effect of strong analgesic agent. The state of so called 'mineralization' brought about by the drug combination, suits excellently to carry out any diagnostic procedure or surgical intervention even if the patient's cooperation is required.

Patients who receive Nitrousoxide and oxygen in addition to neuroleptic and analgesic drugs not only become analgesic and sedated but also lose consciousness or in other words become anaesthetized. The term neuroleptanaesthesia was proposed by Foldes and Kepes (1966) to characterize the state of these patients.

Neuroleptanaesthesia has been in clinical use since it's introduction by De-Castro and Mundeleer in 1959. During this period Droperidol, Fentanyl and Pentazocine have been synthesized and significant advances have been made in understanding neuroleptanaesthesia both physiologically and pharmacologically.

As compared to conventional method of anaesthesia, Neuroleptanaesthesia has been claimed to have minimal systemic toxicity, hepatic functions are not adversely affected (Boger and Tornetta, 1964) and renal blood flow is increased (Gemperle, 1966). There are no observable effects on electrolyte, metabolic acid base balance (Dobkin et al, 1964) and intestinal function (Bergmann, 1965). With the advent of absolutely safe antidote-

Nalorphine in case of Fentanyl, Doxapram in Pentazocine and antiparkinsonism agents in case of the very infrequent extrapyramidal side effects of Droperidol, this technique shows good reversibility and therefore controllability of depth of anaesthesia and has gained much popularity.

Striking cardiovascular stability, seen as a short phase of stabilization after induction, followed by a phase of circulatory stability is maintained throughout anaesthesia (Buhr and Henshel, 1966). As a consequence of alpha-blocking action of Droperidol (Schaper et al, 1963), the peripheral resistance is reduced resulting in a good peripheral perfusion which counteracts the development of metabolic acidosis even in the operation of very long duration.

The antiemetic effects of Droperidol, Fentanyl and Pentazocine is excessively advantageous in the pre and postoperative stages (Aubry et al, 1966 and Crul et al, 1967).

Inspite of high potency and wide safety margin because of high therapeutic index, this technique has disadvantage of significant departure from the most widely practiced technique of balanced anaesthesia, which is easiest for the anaesthesiologist, convenient for the Surgeon but not always in the patient's best interest.

Respiratory depression and ventilatory difficulty are other drawbacks of using this technique but as reported by Foldes et al (1970) the untoward effect of respiratory depression can be overcome by assisting patients spontaneous breathing equivalent to preinduction level. The ventilatory difficulty, can be prevented by very slow infusion of Fentanyl and if it occurs, can be corrected by muscle relaxants (Corssen G. 1966).

Increased expiratory tone and brochoconstriction can also be overcome with narcotic antagonist (Henschel, 1966) like Nalophine but narcotic antagonist also counteracts to variable extent narcotic induced analgesia and hypnosis and their administration causes a sudden decrease in the level of anaesthesia. To minimize this, the smallest dose of antagonist capable of restablishing spontaneous ventilation should be used.

The effects of Droperidol is very long lasting (upto 36 hours) therefore even during the postoperative period the neuroleptic effect persists and often make patient feel uncomfortable. Desired mobilization of patients after certain operation may be delayed by drowsiness, apathy and orthostatic circulatory dysfunction. This undesirable effect may be some what prevented by using only low doses of Droperidol (0.15 mg kg^{-1}) and by avoiding repeated injection.

However in these cases intraoperative neurolepsis may be insufficient specially if the patient is young and vigorous (Kreuscher, 1973).

Although much work has been done so far on neuroleptanaesthesia and analgesia in foreign countries but there is paucity of such studies on Indian subjects. These neuroleptanalgesic agents have recently been introduced in India by Themis Chemicals Ltd.

Keeping in view of the above mentioned advantages and disadvantages it was considered worthwhile to study the cardiorespiratory changes, stability, effectiveness and utilization of Droperidol, Fentanyl, Pentazocine along with their adverse effect if any on healthy patients undergoing major surgery.

REVIEW OF LITERATURE

Until the mid nineteenth century, relief of pain needed during surgery was achieved with natural substances such as alcohol, opium, hyoscine, cannabis indica and occassionally by concussion or suffocation. The problem of inducing quick, safe and easily reversible unconsciousness for any desired length of time in man only began to be solved in the 1840's when nitrous oxide, ether, and choloroform were introduced into clinical practice in rapid succession.

In 1920's ether and chloroform were the main anaesthetic agents used while nitrous oxide and ethyl chloride were often employed for induction. The open drop method was the most popular since the early Boyle's machine which first appeared in 1917, made slow progress.

The use of intravenous anaesthesia dates back to 1872 when Pierre-Cyprien ore used chloral hydrate intravenous hedonal was used in 1905 by Krawkow. Bredenfeld (1916) used intravenous morphine and hyoscine for 'twilight sleep'. Kirschner gave avertin intravenously in 1929. Hexobarbitone was the first drug to make intravenous anaesthesia popular after its use by Weese and Scharpff in 1932. Pentothal Sodium was synthesized by Tabern and Volwiler (1935) and introduced into clinical practice by Lundy of Mayo Clinic in 1935.

HISTORY OF NEUROLEPTANAESTHESIA :

In the above era of mononarcosis the principal requirements of an ideal anaesthetic state were provided by means of inhalation or intravenous anaesthetic drug. On the basis of Woodbridge's (1957) definition of this ideal anaesthetic state, surgical anaesthesia may be attained by providing adequate analgesia, hypnosis, muscle relaxation and protection from neurovegetative reflexes. Obtaining these several effects by means of single volatile or injectable drug could only be possible at the risk of immediate or secondary central or peripheral toxic effects.

So, to avoid these toxic phenomena as far as possible and to ensure the evaluation and control of each of the elements in surgical anaesthesia, the concept of 'potentialized' anaesthesia was brought into light first by combining the curare with the injectable barbiturates (Laborit, 1950 and Huguenard, 1950).

In 1953, DuCailar proposed large doses of ganglioplegics and antihistaminics to complement general anaesthesia, the so called lytic cocktail, to produce a state characterized by marked depression of reflexes and artificial hibernation. Severe fall in blood pressure and variation in individual ability to preserve the vegetative functions and circulatory stability

were instrumental in the failure of this polypharmacological method (Nilsson, 1963).

In 1959 De-Castro and Mundeleer, for the first time proposed to the National French Congress of anaesthesiology the term NEUROLEPTANALGESIA. The goal of this method is to put into practice a more sensitive anaesthesia subtly adopted to each specific case and above all, less depressive and more protective than anaesthesia with a single drug. Neuroleptanalgesia by sparing many of the central nervous system structures and pathway usually blocked by so called orthodox anaesthesia, produces no hypnosis or muscle relaxation but provides intense analgesia and vegetative reflex blockade. This is beleived to result from thalamic analgesia and mental disconnection from the environment but with greater functional integrity of the autonomic centres remaining.

Since 1959 anaesthetists in continental Europe used various combinations of narcotic analgesics and butyrophenones intravenously for surgical anaesthesia (De-Castro and Mundeleer, 1959, Nilsson and Janssen, 1961).

In 1963 Nilsson, proposed the concept of obtaining selective nervous system sedation and pain relief without the use of barbiturates or volatile inhalational anaesthetic agents by combining a morphomimetic and a neuroleptic drug.

Most anaesthesiologists have intended to regard this technique as a way to supplement established anaesthetic methods and become useful addition to the practice of balanced anaesthesia rather a new type of anaesthesia (Spoerel and Chan, 1965).

NLA-I REGIME :

Neuroleptanalgesia has been in clinical use since its introduction with Haloperidol and phenoperidine described as NLA formula-I. In Britain an early report (Brown and Horton, 1963) on its use with light general anaesthesia for neurosurgical procedures claimed that it constituted a major advance in anaesthesia for operations lasting longer than 1 hour. But its general spreading was hampered by the side effects appearing quite often namely, profound hypotension, extrapyrmidal disturbances and in a few instances prolonged post-operative psychic changes ranging from diminished power of concentration to hallucination which were mostly due to cumulation of the analgesic (phenoperidine) and neuroleptic (haloperidol) used. So this drug combination had not permitted to proceed with neuroleptanalgesia with an appropriate safety.

NLA-II REGIME :

Droperidol and Fentanyl, synthesized by Janssen and put on the market by chemical works of Godeon

Richter Ltd., were found practically free from the aforesaid disadvantages. Due to the harmlessness their large spectrum of efficiency and easiness of dosage these drugs are considered superior to NLA-Formula-I.

Patients who received Oxygen and nitrous oxide in addition to Droperidol and Fentanyl not only attain analgesia and sedation but also lose consciousness or in other words become anaesthetized. The term neuroleptanaesthesia was proposed by Foldes and associates in 1966 to characterize the state of these patients.

Neuroleptanaesthesia induced with a fixed 50:1 mixture of Droperidol and Fentanyl citrate, nitrous oxide and Oxygen rapidly became a widely used anaesthetic technique.

Holderness and Chase (1963) used dehydrobenzperidol and Phentanyl in 400 cases and found cardiovascular stability but have reported sharp fall of blood pressure in 1 patient and gradual fall of systolic blood pressure of approximately 25% of the preoperative level in 22 cases. Reduction in rate and depth of respiration occurred maximum during induction associated with rigidity of skeletal muscles in 8% of cases. Emergence from anaesthesia was smooth, consciousness and orientation returned soon after the discontinuance of nitrous oxide, post-operative nausea occurred in

23 patients and post-operative analgesic requirement was less.

Corssen, G (1966) used Innovar in doses of 1 ml per 10 lbs. of body weight in 510 poor risk patients and found it sufficient to induce and maintain anaesthesia for several hours. This general dose schedule was increased or decreased according to the anaesthetic risk. Besides apnoea or marked respiratory depression accompanied by chest wall rigidity other complications included transient hypotension (82 cases), extrapyramidal muscular twitchings (5 cases), post-operative emesis (4 cases) and increased systolic and diastolic blood pressure (2 cases).

It seemed probable (Foldes et al, 1964) that the complications associated with neuroleptanaesthesia might be due to clinicians uncritical acceptance of the 50:1 fixed mixture of Droperidol and Fentanyl. This mixture was introduced into anaesthetic practice without the prior investigation of the pharmacological effects of its individual components in man. Consequently before attempting to develop a trouble free widely applicable technique of neuroleptanaesthesia it seemed essential to investigate the pharmacological effects of Droperidol and Fentanyl in human subjects.

The results of clinicopharmacological studies by Foldes et al (1966) indicates that the administration

of a fixed mixture of the slow acting and long lasting Droperidol and fast acting and shortlasting Fentanyl, is pharmacologically unsound. It also becomes evident that the ventilatory difficulty encountered during anaesthesia were due to overdoses with Fentanyl and late extrapyramidal excitation observed after neuroleptanalgesia was probably caused by the unnecessarily large doses of Droperidol used. It was therefore decided (Foldes et al, 1966) to develop a technique of neuroleptanaesthesia based on the administration of a single dose (0.15 mg/kg) of Droperidol followed by intravenous injection of repeated small doses of Fentanyl which in conjunction with the nitrous oxide and oxygen would provide adequate anaesthesia without apnoea or undue depression of the respiratory rate. Muscle relaxants were to be used only for endotracheal intubation and to provide surgical relaxation without total paralysis of respiratory muscles. It was expected that by assisting spontaneous ventilation at the rate and rhythm determined by the patient and tidal volume by anaesthetist, ventilatory difficulty during anaesthesia could be prevented and by using only a single moderate dose of Droperidol, the post anaesthetic extrapyramidal excitation could be avoided.

Schotz and Zeigler (1967) used controlled technique with a dilute intravenous drip of Innovar to obtain a steady state in patient with high metabolic rate and increased tolerance and found reduction in total dose required as well as their disadvantages.

Foldes (1970) attempted to replace Droperidol with other ataractic drugs for example largactil, trifluprómazine and hydroxyzine but were unsuccessful. However they could obtain satisfactory neuroleptanaesthesia with the use of meperidine, alphaprodine or morphine sulphate instead of Fentanyl employed in conjunction with Droperidol. Their study indicated that Fentanyl did not seem to offer any significant advantage over meperidine except for a lower incidence of apnoea and more rapid recovery of consciousness at the termination of anaesthesia.

Kay and coworkers (1970) recommended Pentazocine as a suitable alternative for Phenoperidine in combination with Droperidol in neuroleptanalgesia for neuroradiological procedures because of its fewer cardiovascular changes and less respiratory depression.

Iwatsuki and associates (1971) had applied this modified method in more than 800 cases. The results were compared with those of original method using Droperidol and Fentanyl. This study indicated the usefulness of pentazocine as an analgesic component

in neuroleptanalgesia. The modified method using Droperidol and pentazocine produced smooth induction of anaesthesia, stable cardiovascular state during surgery, rapid recovery from anaesthesia and physical and mental quiteness in post-operative period with minimum incidence of nausea and vomiting. A lack of severe respiratory depression and ventilatory difficulty due to muscle rigidity was another advantage of this modified method over the original one. It is also convenient for clinical practice that the analgesic used is not a narcotic. However the respiratory depression produced by pentazocine can be easily antagonised by Doxapram (Yamato, 1973) without affecting its analgesic effect.

Foldes (1972) used Droperidol in combination with monoanaesthetic Ketamine to prevent or to diminish unpleasant dreams during recovery.

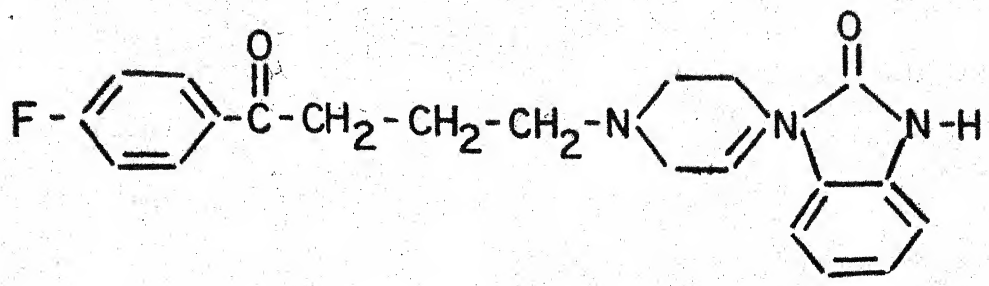
PHARMACOLOGICAL EFFECTS OF NEUROLEPTANALGESIC DRUGS

DROPERIDOL

Droperidol is a neuroleptic drug of the butyrophenone series which includes Haloperidol and Trifluperidol (Janssen P.A.J., 1966).

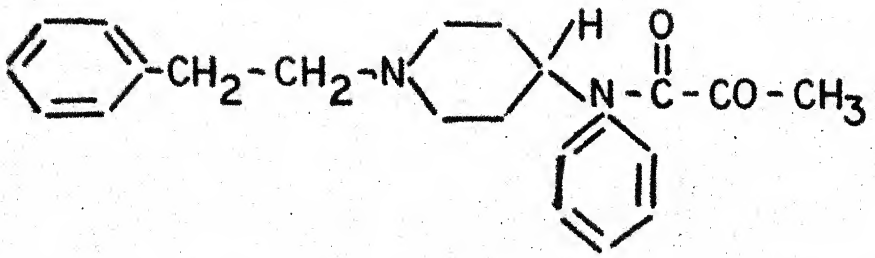
Chemical Formula : $C_{22}H_{22}FN_3O_2 = 379.42$

Chemical Name : 1-(1-3-(p-fluorobenzoyl)-1,2,3,6-tetra-hydro-4-pyridyl)-2-benzimidazolinone.



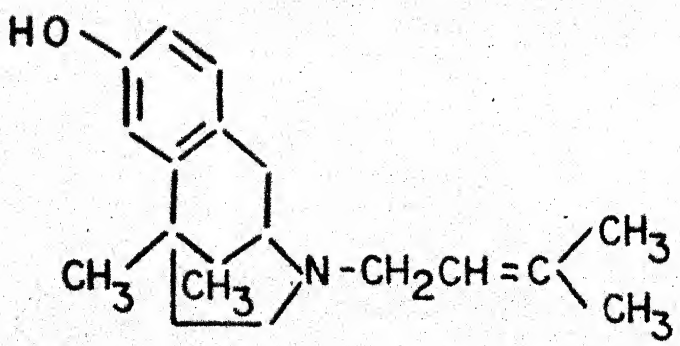
DROPERIDOL

FIG. NO.-1



FENTANYL

FIG. NO.-2



PENTAZOCINE

FIG. NO.-3

Structural Formula : Figure No. 1

Signs of general anaesthesia :

Following intravenous administration of Droperidol there is a rapid induction of neuroleptic state. The term neurolepsis was first introduced by Delay and Deniker (1961), characterized by lack of initiative, disinterest in surroundings with conservation of conditioned response. Patients can be easily aroused and is obedient to commands.

The action starts within 2 to 3 minutes, is maximum after 10-12 minutes and persists for 6-8 hours (Janssen, 1966). It potentiates the effects of thiopentone. In association with thiopentone sleep time is doubled (Dobkin and associates, 1964).

Effect on component of neuron :

(a) Peripheral receptors : There is a weak antihistaminic action (Haase and Janssen, 1965).

(b) Afferent and efferent system : Extra-pyramidal seizures have been observed but these are relatively rare even when large doses are employed (Brown, 1964). Holderness and associates (1963) have observed extrapy-ramidal tract reaction such as oculogyric crisis in infants and children following a single dose of 1.2 mg per 10 lbs. of body

weight. This occurred after the sedative effect had disappeared usually 12-18 hours after injection. Corssen et al (1964) observed muscle jerking and twitching in three patients shortly after injection of Innovar. Tornetta et al (1969) reported 17 patients in whom acute rigidity of facial, mandibular and pharyngeal muscles, developed in the immediate post Innovar injection period, occassionally interfering with ventilation. Janis (1972) reported sustained and rapid development of an acute severe stiffness of neck and back muscles with facial grimace without chest wall rigidity or ventilatory impairment following premedication with Innovar intravenously. Most extra-pyramidal reactions caused by Droperidol are of dyskinetic type usually occurs in recovery period. These extra-pyramidal tract reactions tend to disappear following administration of benztropine or atropine (Patton, 1975).

Effect on autonomic nervous system :

There is an adrenergic blockade with a resulting decrease in peripheral resistance. Droperidol minimies the rise in blood pressure caused by intravenous epinepherine and non-epinephrine (Holderness and

associates, 1963). In addition, Droperidol prevented ventricular arrythmia induced by epinephrine given intravenously in dogs anaesthetized with pentobarbital. This blocking effect is due to an unclassical alpha-blocking action effecting epinephrine (Janssen et al, 1963; Schaper et al, 1963; Yelnosky et al, 1963; Whitwam and Russell, 1971). Droperidol offers protection from surgical stress (Ferrari and Stephen, 1966) and provides optimal tissue perfusion (Corssen, 1966) by selectively blocking the alpha-receptors of the sympathetic nervous system and therefore suppressing the vasoconstrictive action of Catecholamines. However, in the isolated rabbit ear artery, Droperidol was reported to cause a non-specific inhibition of vasoconstriction responses and its adrenergic blocking properties has been questioned (Puddy, 1971).

Greene (1972) reported that solvents and preservative used with droperidol are partly responsible for its alpha-adrenolytic action but again it was confirmed that Droperidol have alpha-adrenergic blocking property in isolated blood vessel of the dog (Muldoon et al, 1977).

Droperidol has been used as an antishock drug on the basis of there being 10% increase in epinephrine level associated with shock (Mc-Neil, 1963). Due to its alpha-receptor blocking and tissue perfusion

improving effects, the drug can be widely applied with good result in the complex attendance of shock conditions of various origin. Because of the demonstrable lack of increased skin temperature it was felt that the increased flow probably occurs in muscles or arterial venous shunts (Schaper, 1963). There is no anticholinergic effect (Haase and Janssen, 1965).

Effect on respiration :

The effect of Droperidol on respiration is slight (Yelnosky et al, 1963 and Schaper et al, 1963) by increasing respiratory volume relatively high dosage of Droperidol improve effective ventilation and oxygen saturation. Prys-Roberts et al (1967) have shown that neurolepts do not potentiate the ventilatory depression of analgesics used concurrently in neuroleptanaesthesia although the combination produces more sedation than either neuroleptic or analgesic agent when used alone.

Effect on circulation :

The Cardiovascular system is stable with only a slight fall in blood pressure due to reduction in peripheral vascular resistance, secondary to alpha-adrenergic blockade and also to direct peripheral vaso-dialatation. Dobkin et al (1964) treated 16 healthy volunteers with a 10 ml combination of 1 mg ml^{-1} Droperidol and 0.02 mg ml^{-1} Fentanyl and found

that "in most subjects the cardiovascular system remained remarkably stable during the action of this agent". There is no direct myocardial depression (Corssen, 1964) and the cardiac out put is increased (Haase and Jonssen, 1965).

MacDonald and colleagues (1966) have measured changes of cardiac output during neuroleptanalgesia but did not consider changes to be significant clinically. Serious circulatory disturbances were not found following pre-medication with neuroleptic drug other then pre-disposition towards postural hypotension (Prys-Roberts and Kelman, 1967).

Droperidol increases the heart rate, coronary blood flow and left ventricular Oxygen consumption, while mean aortic pressure is considerably reduced. These effects are due to a fall in systemic vascular resistance caused by partial blockade of adrenergic alpha-receptors. The increase in heart rate mainly accounts for the enhanced myocardial consumption of Oxygen after administration of Droperidol. Compared with this the rise in cardiac index that results from the increase in heart rate is only of minor importance for the elevated oxygen demand (Sonntag, 1973).

Brain circulation and metabolism :

Nilsson and Ingvar (1966) studied the cerebral

blood flow during neureleptanaesthesia in cats and reported that Droperidol causes an increase in cerebral blood flow upto 76% and it may induce epileptic seizures because of increase in cerebral metabolism secondary to increased blood flow. On the contrary, Michenfelder and Theye (1971) have reported that Droperidol do not significantly alter cerebral oxygen consumption but results in gradual decrease in cerebral blood flow to 60% of control due to increase in cerebrovascular resistance. Thus, cerebral blood flow although reduced is adequate to meet normal aerobic metabolic requirements in the presence of normal haemoglobin and oxygen level.

Effect on digestive tract :

Halpern and Ducrot (1946) observed a motor depression of the digestive tract following therapeutic doses of psycholeptic drugs. On the basis of these studies Bergmann (1965) suspected that dehydrobenz-peridol would have an inhibitory effect on intestinal motility and he undertook extensive and precise studies which led to the conclusion that innovar has no appreciable effect on intestinal function.

Antiemetic action :

Dobkin et al (1964) found that "the absence of vomiting during recovery was outstanding". Aubry et al (1966), Vandewalle (1967) and Crul et al (1967) experienced antiemetic effects of Droperidol. After

endoscopies and various important surgical interventions performed in neuroleptanaesthesia they claimed less than 1% incidence of nausea and vomiting. The overall incidence of nausea and vomiting in the study of Prys-Roberts and Kelman (1967) on 230 patients anaesthetized with neuroleptanaesthesia was only 4.4% in fentanyl group providing marked antiemetic effect of butyrophenones. The potent antiemetic effect of Droperidol eliminates vomiting during induction and maintenance of anaesthesia (Corssen, 1966).

Effect on Hepatic Function :

Tornetta and Boger (1964) observed its effect on the state of liver by the serial control of 13 liver function tests (serum bilirubin, prothrombin time, alkaline phosphatase, SGOT, SGPT, BSP retention and Serum cholesterol etc.) and reported no significant deviation.

Action at Cellular Level :

The mode of action of neuroleptic drug is believed (Edmonds et al, 1970) to depend on their ability to form a monolayer on certain biological membranes which act as a lipid water interphase. In this way they decrease the permeability of membrane by reducing its surface tension in a manner similar to soap and detergents (Seeman and Bailey, 1963). The action is known to be specific for cell membrane in

central nervous system excited by dopamine, noradrenaline and 5 HT. The permeability of such post synaptic membrane is normally regulated by the competetive inhibition of glutamic acid by gamma amino-butyric acid (Janssen, 1965). There is structural similarity between GABA and neuroleptics, the basis of which is the basic nitrogen linkage to an S-shaped 4-carbon atom chain. Janssen (1967) has proposed that by occupying GABA receptors on the postsynaptic membrane the neuroleptic drug decreases synaptic transmission and lead to a build up of the transmitter in the intersynaptic cleft. Neuroleptics also inhibit the reuptake of dopamine and noradrenaline into the storage granules of the presynaptic terminals particularly when the concentration of these is increased following treatment with M.A.O. inhibitors (Roos, 1965; Janssen, 1967) but they do not influence the deletion of cerebral noradrenaline induced by reserpine. Recent evidence suggests that although there is a storage correlation between the inhibition of amine uptake and the inhibition of operent behaviour induced by neurolepts no casual relationship has been established between the two phenomena (Dresse, 1967).

Neuroleptic drugs have a prediliction of certain areas of the brain known to be rich in dopaminergic synapses specially those of the C T zone of Borison

and Wang (1956) and the extrapyramidal-nigrostraitum system related to operent behaviour (Hillarp, Fuxe and Dahlstrom, 1966).

FENTANYL

Fentanyl is a potent analgesic drug of the 4-aminopiperidine series (Janssen, 1962). The product is available as citrate.

Chemical Formula : $C_{22}H_{28}N_2O$ = 336.46

Chemical Name : 1-(phenethyl-4-(N-propionylanilino) piperidine citrate.

Structural Formula : Figure No.2

Signs of general anaesthesia :

It is 100 times more powerful than morphine miligram for miligram (Yelnosky and Gardocki, 1963). There is peak intensity of action (analgesia, respiratory depression and tranquility), appearing sooner than most narcotic analgesics after intravenous or intramuscular injection. The onset of action is usually within 2-5 minutes (Holderness and associates, 1963; Dobkin and coworkers, 1964), the duration of action is 30-45 minutes. The duration of respiratory depression is also less than most narcotic analgesics. Both the rate and depth of respiration may decrease, apnoea may appear. Its potency is 350-1000 times the potency of meperidine (Larson, 1963). All the action of fentanyl seem to be effectively antagonised by nalorphine or levallorphan (Foldes and others, 1965).

Effect on Component of Neurons :

Fentanyl depresses selectively the functional activity of those areas of brain stem which are concerned with a severe degree of respiratory depression. This respiratory depression is of such a nature that the automatic element of respiration fades out but the conscious patient nevertheless remains capable of breathing on command. This pharmacological effect is attributed to a gross or total loss of sensitivity to Co_2 in the respiratory centre. Despite this, function of reticular activating system is well preserved to maintain the consciousness (Hagoun, 1963).

Fentanyl blocks pain at the thalamic level with little effect on the cortex (McNeil, 1963), however work with stereotactic surgery has led to the observation that cortical stimulation of Brodman's area causes a form of apnoea which can be corrected by asking the patients to breath. The same may occur with electrical stimulation of hippocampus (Dilagne, 1961).

Effect on autonomic nervous system :

Fentanyl has central vagal stimulant action which explains bradycardia and sweating (Holderness and coworkers, 1966). Both of which are reduced or eliminated by the preoperative administration of atropine in doses commonly used. There is no evidence of histamine release after Fentanyl (Dobkin and coworkers, 1965).

Effect on Brain Circulation and metabolism :

According to Brown (1964) Fentanyl does not produce cerebral vasodilation but it decreases the cerebral blood flow probably secondary to increase in cerebro-vascular resistance (Michenfelder and Theye, 1971).

Effect on Respiration :

Fentanyl produces marked respiratory depression. This effect appears in 5-10 minutes and lasts for 15-60 minutes after administration. The maximum peak effect is for 15-30 minutes. Both the rate and depth of respiration are decreased. Apnoea is shorter than the duration of analgesia (Nilsson, 1963; Dobkin and coworkers, 1964; Corssen and coworkers, 1964).

Profound ventilatory depression is a feature of narcotic analgesics which can not be separated from the analgesic action and may be manifested in number of ways. In conscious patients it causes a decrease in expiratory minute volume, rather than in the frequency of breathing (Jennett et al, 1968), since the changes are related to decrease in Oxygen consumption and Co_2 production.

The character of ventilatory depression was different when Fentanyl was administered to patients anaesthetized with 70% nitrous oxide and 30% oxygen (Prys-Roberts and Kelman, 1967). According to their

observations frequency of breathing is significantly reduced, minute volume and alveolar ventilation may fall despite a compensatory increase in tidal volume, thus alveolar Pco_2 tends to rise. The duration of raised $PACo_2$ is dose dependant and lasts for 15-30 minutes. Although the ventilatory depression occurring during neuroleptanaesthesia may be prolonged into the post anaesthetic period, the blood gas tension, acid base state after neuroleptanaesthesia do not differ significantly from those found after other anaesthetic techniques.

Although Fentanyl is considered to be a short acting narcotic analgesic (Romagnoli, 1973) but there are reports (Becker et al, 1976) of prolong and recurrent ventilatory depression in patients who have been given Fentanyl during general anaesthesia.

Studies in dog by Hug and Murphy (1979) suggest that the short duration of action of Fentanyl after a single moderate dose is due to its rapid redistribution from brain to other tissues and that repeated or large doses leads to accumulation of Fentanyl and consequently ventilatory depression. Later on Meclain and Hug (1979) suggested that Fentanyl accumulation may be associated with cumulative respiratory effects since there appears to be a close correlation between plasma level of Fentanyl and ventilatory depression in man. So the

anaesthesiologist should be aware of this potential for prolonged ventilatory depression from this short acting narcotic analgesic.

Respiratory depression is easily controllable. There is marked dissociation between the depression of respiratory and cortical areas, so that even apnoeic patients remain completely conscious and respond adequately to verbal instructions to breath (Corssen et al, 1964) controlled respiration provides effective ventilation, without loss of analgesia (Prys-Roberts et al, 1967).

Nalorphine rapidly and completely reverses the respiratory depressant effect of Fentanyl (Prys-Roberts et al, 1967, Foldes et al, 1965).

Following a rapid intravenous injection of 0.1 mg of Fentanyl, there may be marked rigidity of the muscles of the arm, legs, abdomen and thoraz, which makes ventilation of the patients difficult (Holderness and coworker, 1963). Corssen (1966) however observed that "although this period does not last more than 3 to 5 minutes and subsides spontaneously it can be readily overcome by I/V administration of succinylcholine."

Kim Comstock et al (1979) studied the incidence of muscle regidity and magnitude of hypercarbia during induction of Fentanyl - Oxygen anaesthesia, which showed high incidence of chest and abdominal wall rigidity and

in-ability to ventilate adequately thus resulting in progressive hypercarbia. Loss of consciousness and onset of muscle rigidity occurred at about the same time and dictated neuromuscular blockade in high percentage of patients in order to provide adequate ventilation.

There may be bronchoconstriction due to increased vagal tone (Holderness and coworker, 1963). If bronchoconstriction occurs the technique can be abondoned and anaesthesia can be continued with halothane or ether. If these are contraindicated, the bronchoconstriction can be treated by intravenous infusion of a dilute (1-2 mg per 100 ml) solution of isoproterenol hydrochloride (Foldes and others, 1966).

Effect on Circulation :

Fentanyl had been observed to cause hypotension (Larson, 1963; Gordocki and Yelnosky, 1964; Gorodetzky and Martin, 1965). It is generally considered to have very little influence on the heart and circulation (Shephard, 1965), apart from inducing a fall in systemic blood pressure which lasts for few minutes (Brown, 1965). However, the hypotensive effects of the drug following clinical dosage were not observed by Holderness, chase and Dripps (1963).

Mac Donald et al (1966) observed occurrence of raised cardiac output, central venous pressure and

mean arterial pressure simultaneously with an increase in $FE'Co_2$ which resemble the changes occurring with deliberate hypercapnoea during spontaneous ventilation rather than a direct effect of the analgesic drug. He has measured the changes of cardiac output during neuroleptanalgesia but did not consider the changes to be clinically significant.

By measuring the cardiac output and other haemodynamic variables Prys-Roberts and Kelman (1967) reached to the same conclusion as that of MacDonald, that is, cardiovascular effect of the analgesics were modified by alteration in ventilation, in particular with haemodynamic effects of concurrent hypercapnoea. Good cardiovascular stability after Fentanyl administration was also demonstrated by Tammisto et al (1970).

Robert K. Stoelting (1975) used high doses of Fentanyl with oxygen as an effective technique in patients with valvular and coronary artery disease undergoing elective open heart operation, since it minimizes alterations in cardiovascular dynamics. He noted increase in central venous pressure during drug infusion which decreased to awake level following controlled ventilation and skeletal muscle paralysis reflecting thoracoabdominal muscle rigidity rather than circulatory response. In patients with septic shock undergoing abdominal surgery, Stanley and

Reddy (1979) reported that large doses of fentanyl and oxygen produce complete anaesthesia but no cardiovascular depression.

PENTAZOCINE

Pentazocine is a benzomorphan derivative and a mild narcotic antagonist. It has recently been introduced as a potent analgesic. This drug is of great clinical interest because of the W H O's recommendations (1969) that at present it should not be subject to narcotic control. Since May, 1971' the drug is not under D.D.A. regulations.

Chemical name : (1.2.3.4.5.6-hexa hydro-3-(3-methyl-2 butenyl)-6,11-dimethyl-2,6-methano-3-benzazocin-8-01).

Pentazocine was synthesized at the Sterling Winthrop research institute in 1959. This compound was the result of search for a drug which did not have significant addictive potential and would be active when tested for its analgesic activity in man. This search gained momentum in 1954 as a result of report by Lasagna and Beecher, who observed that the potent narcotic antagonist nalorphine was equally potent analgesic as morphine. This observation was later confirmed by Keats and Telford (1957). While nalorphine appeared to be devoid of the addictive potential which exists for the narcotics, its dysphoric and

psychotomimetic effects inhibited its use as an analgesic. So the search continued for the compound which had weak narcotic antagonist activity in laboratory animals retaining potent analgesic action in man and devoid of addictive potential. Pentazocine appears to be the right drug fulfilling all the ideal requirements.

Pentazocine can be useful supplement to nitrous oxide-oxygen anaesthesia and that general anaesthesia potentiate the respiratory depression produced by Pentazocine. The onset of analgesic action is approximately within 2-3 minutes when given intravenously and 15-20 minutes when given by intramuscular route. The action lasts for about 3 hours (Tammisto et al, 1970).

Relative potency of Pentazocine and other analgesics :

One of the earliest studies of the effect of Pentazocine on post-operative pain was that of Keats and Telford (1964) who reported that 10-20 mg/70kg body weight of Pentazocine given intramuscularly produced analgesia equivalent to 10 mg/70kg body weight of morphine.

In a study of 2190 post-operative patients Gordon and Moran (1965) found 30 mg Pentazocine to be equianalgesic to 10 mg of morphine or 75 mg of meperidine but Guldmann (1969) on the contrary found that 20 mg of Pentazocine had better analgesic action than 100 mg of meperidine.

Plasma concentration of Pentazocine correlates well with the onset, duration and intensity of action. After intravenous injection the peak of the brain concentration occurred within 10 minutes, at the time of peak concentration 10% of injected dose was in the brain while the corresponding value at 60 minutes was 2% (Coroneos and colleggues, 1974).

Effect on respiration :

Pentazocine shares with other strong analgesic drugs in the tendency to depress respiration as measured by changes in minute volume, arterial carbondioxide tension and end tidal carbon-dioxide tension, steady state carbon-dioxide responses and rebreathing carbon-dioxide response curve, (Davie et al, 1970).

The respiratory effect of Pentazocine has been compared with Phenoperidine in healthy volunteers by Jennett, Barker and Forrest (1968) who found that both drugs in approximately equipotent doses (Pentazocine 20 mg, Phenoperdine 1.5 mg) produced similar increase in $PACo_2$ of the order of 5 mm of Hg. but relative absence of disturbance in breathing pattern by Pentazocine is a striking feature. Kay and coworkers (1970) observed that respiratory depression was more persistent and disturbing to the patient both subjectively and as reflected in whole body oxygen

consumption with phenoperidine than that produced by Pentazocine. They found fall in respiratory rate and arterial oxygen tension similar for both drugs but the increase in $PaCo_2$ greater and more persistent with Phenoperidine.

The respiratory depression can be significantly reversed by the nonspecific analeptics methylphenidate or Doxapram (Telford and Keats, 1965) and by potent narcotic antagonist nalaxone (Kallos and Smith, 1968).

Effect on cardiovascular system :

Pentazocine differs in its cardiovascular effects from the classical morphine pattern of hypotension and braydcardia. Most investigators (Sadove et al, 1964; Ahlgren and Stephen, 1966; Norris and Telfer, 1968) have observed a rise in blood pressure accompanied by a slight tachycardia in conscious patients after pentazocine. Although Keats and Telford (1964) only encountered hypertensive effect at high dose levels in conscious patients (2 mg/kg) as did Brown (1969). Potter and Payne (1970) observed a significant rise in mean arterial pressure of 9.5 $\pm$ 4.9 mm of Hg with a dose level of 30 mg given intravenously to conscious adults. This hypertensive effect is unlikely to be related to hypercarbia since its onset was too rapid and similar rise had been recorded during ventilation when the Pco_2 was constant by Tammisto and others (1967).

Potter and Payne (1970) also observed a similar pressor response when Pentazocine was given intravenously during anaesthesia with nitrous oxide and halothane but in contrast to the effects on conscious patient the pressor response was preceded by a transient period of hypotension which was accompanied by a slight bradycardia that persisted into the pressor response.

Davie, scott and Stephen (1970) reported an early transient fall in cardiac output after Pentazocine in patients anaesthesized with halothane. Simultaneously there occurred a sharp sustained rise in central venous pressure followed by a slight rise in mean arterial pressure. The cause of this hypertensive effect whether increased peripheral resistance or increase cardiac output is not well established (Tammisto and colleagues, 1970) but the pallor observed after higher doses argues in favour of the former mechanism.

However Kay and coworker (1970) did not observed any systemic hypertensive response when they used Pentazocine in conjunction with Droperidol as a modified technique of neuroleptanalgesia, which they say might be due to alpha-receptor blockade produced by Droperidol, confirming the views of previous investigators (Tammisto and colleagues, 1970) of the direct action of the drug on the arterial blood vessel. Any vasoconstriction of the pulmonary artery tree which

may possibly occur following Pentazocine would also be blocked since MacDonald and associate (1966) recorded a fall in pulmonary artery pressure following injection of Droperidol.

Effect on other organs :

Pentazocine seems not to have any deleterious effect on the blood picture or liver functions (Flavell Matts and others, 1969). Sigman and Elwood (1967) have reported that intramuscular injection of 30 or 60 mg of Pentazocine to normal subjects did not cause a significant change in glomerular filtration rate but both doses caused a decrease in effective renal plasma flow.

Side effects :

The side effects of Pentazocine resemble those of other narcotic analgesics and include nausea, vomiting, drowsiness, dizziness, sweating, rarely euphoria and headache (Keats and Telford, 1964). Occassionally psychotomimetic reactions with hallucinations and unpleasent dreams have been reported at high dose levels by Hamilton et al (1967).

Pharmacological effects of Narcotic antagonist

Specific antagonist - NALORPHINE :

Nalorphine is a specific narcotic antagonist, was first described in 1915 by Pohl. The clinical significance of its antagonistic effect was not explored until 1951 when Eckenhoff et al reported the use of nalorphine

as an antidote to morphine poisoning in man. Wikler and associates (1953) demonstrated that nalorphine precipitates acute abstinence syndrome in postaddicts who had received morphine, methadone or heroin for brief period.

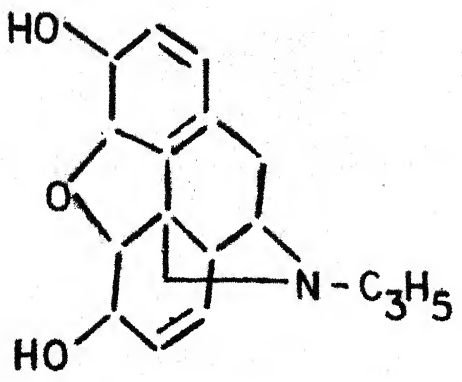
Chemical Name : n-allylnormorphine hydrobromide

Structural Formula : Figure No. 4

The most striking property of nalorphine is its marked ability to prevent or promptly abolish many of the actions of Morphine. Narcotic induced euphoria, analgesia, drowsiness, respiratory depression, muscle incordination, depression of polysynaptic reflexes, vomiting, defecation, bradycardia, hypothermia, suppression of ACTH release, antidiuresis, miosis, hyperglycaemia and gastrointestinal spasm are all antagonised. Within 1-2 minutes after intravenous injection of 5-10 mg of nalorphine, there is prompt increase in respiratory minute volume, and Pco_2 decreases towards normal. If blood pressure is decreased, it tends to return towards normal. Antagonism of narcotic induced respiratory depression usually lasts for 1-4 hours (Woods, 1956).

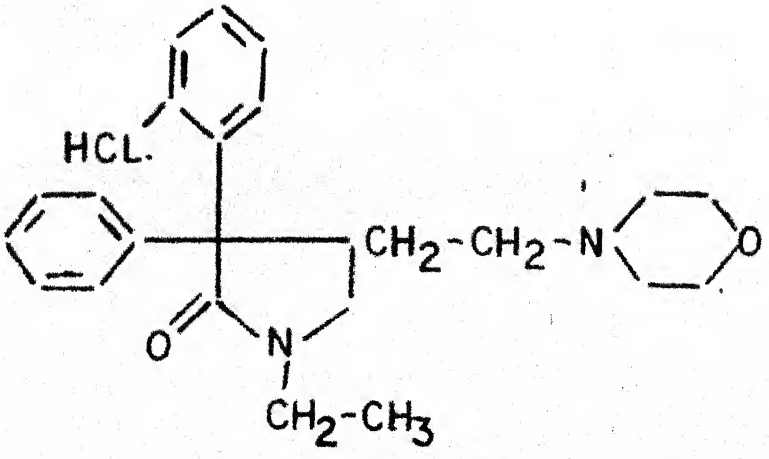
Non specific antagonist - DOXAPRAM :

The doxapram an analept, introduced by Lunsford et al (1962) is reported to reverse post-operative hypoxia and hypercapnia. It is advocated for the therapy of respiratory failure resulting from chronic pulmonary disease where oxygen therapy may be expected to



NALORPHINE

FIG. NO.- 4



DOXAPRAM

FIG. NO.-5

exaggerate hypercapnia and acidosis (Winnie et al, 1971). Unlike other analeptic agents Doxapram has a large margin of safety, the therapeutic ratio (Convulsive dose upon ventilatory stimulating dose) is about 20-40, compared with 2-4 for other analeptic agents suggesting that doxapram has a direct selective stimulatory effect on respiratory neurons at doses that do not stimulate nonrespiratory units (Funderburk et al, 1966). But Wang and Hirsh (1973) have suggested that the primary site of action of doxapram is on carotid chemoreceptors whereas Scott, Whitwam and Chakrabarti (1977) said that Doxapram produces respiratory stimulation mediated through the peripheral carotid chemoreceptors and as the dose level is increased, the respiratory centre in the medulla is stimulated with progressive stimulation of other parts of the brain and spinal cord.

Chemical Name : 1 ethyl-4-(2-(4 morpholinyl) ethyl)-3, 3-diphenyl-2-pyrrolidinone hydrochloride.

Structural Formula : Figure No. 5

The onset of respiratory stimulation following the recommended single intravenous injection usually occurs in 20-40 seconds with the peak effect at 1-2 minutes. The duration of effect may vary from 5-12 minutes (Gupta and Dundee, 1974). The respiratory stimulant action is manifested by an increase in tidal volume associated with a slight increase in respiratory rate.

Doxapram counteracts the respiratory depressant effect of morphine without abolishing analgesic effect. Since it is quickly metabolized the effect is short lived so the immediate post operative period is crucial to the latter development of chest problem (Gawley et al, 1976).

Sakuraya and Fujita (1974) noted the ionotropic effect of Doxapram hydrochloride on cardiac performance when given during emergence from neuroleptanaesthesia confirming the finding of Wakushima and coworkers (1974) who observed increase in heart rate and systolic and diastolic blood pressures when Doxapram was injected during the recovery period. They also found significant increase in tidal volume but not in respiratory rate. There was increase in Pao_2 and fall in $PaCo_2$ resulting in shift of blood pH towards alkalosis. The side effects of Doxapram viz. diaphorism and dyspnoea were observed in few cases when the drug was administered rapidly in patients who had laparotomy under neuroleptanaesthesia with Droperidol, Pentazocine and Nitrous Oxide.

MATERIAL & METHOD

SELECTION OF PATIENTS :

This study is based on the healthy patients (Grade I and II, A.S.A. classification) admitted in Medical College Hospital, Jhansi, undergoing all types of major surgical procedures, except caesarean section because of high risk of foetal respiratory depression.

These patients were divided into three groups A, B and C and each group was subjected to the different combination of neuroleptanalgesic drugs.

The patients of group A were given Droperidol and Fentanyl (THEMIS CHEMICALS LTD.).

The patients of group B were given Droperidol and Pentazocine (RANBAXY LABS.).

The patients of group C were given Droperidol Fentanyl and Pentazocine.

PREPERATION OF PATIENTS :

A thorough preanaesthetic check up was done specially to exclude any cardiovascular, respiratory, neurovegetative diseases and supplimented by routine and special investigations as and when needed. Following parameters such as pulse rate and rhythm, blood pressure, respiratory frequency, tidal volume and minute volume were checked and recorded. Informed consent for general anaesthesia was taken. All patients were kept fasting for 6-8 hours.

PREMEDICATION OF PATIENTS :

All patients were premedicated 1 hour before surgery with 2.5 mg. Droperidol, 0.05 mg. Fentanyl (Group A and C) or 30 mg Pentazocine (group B) and Atropine 0.3 mg to 0.6 mg given intramuscularly.

TECHNIQUE :

Patients were connected to electrocardiograph oscilloscope and autorecorder before induction of anaesthesia. Slow intravenous infusion with 5% dextrose started.

Now Droperidol in doses of 0.15 mg kg^{-1} to 0.18 mg kg^{-1}, was administered slowly intravenously and surgeon was asked to prepare the operative field.

To produce partial denitrogenation a high flow of 100% Oxygen was administered through a face mask for about 3 to 5 minutes, then the inhaled gas mixture was changed to nitrous oxide 6 litres $minute^{-1}$ and oxygen 2 litres $minute^{-1}$.

After 7 to 10 minutes of injecting Droperidol, Fentanyl in doses of 0.003 mg kg^{-1} to 0.004 mg kg^{-1} to group A and group C or Pentazocine 1.2 mg kg^{-1} to group B was given intravenously very very slowly. As the patient become unconscious, Succinylcholine was given to facilitate endotracheal intubation. After another 20 to 40 seconds, when mild faciculations caused by succinylcholine had ceased, lungs were inflated with

100% Oxygen through face mask. When the patient was found completely apnoeic and relaxed, direct laryngoscopy was done, 3 to 4 ml of 4% Lignocaine was sprayed on the mucous membrane of pharynx, larynx, and trachea by laryngeal spray, entotracheal tube of the largest possible size was passed and connected to Boyle's mark III anaesthetic machine, through Magill semiclosed circuit using non-rebreathing Rubin valve. The flows of nitrous oxide and Oxygen were changed to 5 litres minute^{-1} and 3 litres minute^{-1} respectively. Ventilation was controlled till the return of spontaneous respiration, then it was assisted. Now surgeon was asked to give incision and if patient responded to surgical stimulus manifested in the form of increased pulse rate, respiratory frequency, blood pressure and sweating or movement of toes and fingers, Fentanyl 0.025 to 0.05 mg in group A and group C or 10 to 20 mg Pentazocine to group B was given intravenously to obtain satisfactory analgesia.

When muscle relaxation was needed for the provision of good operative conditions or when there was difficulty in ventilation because of rigid chest wall, flaxedil or tubarine was given in subapnoeic dose and ventilation was assisted.

As the signs of subsiding of analgesia appeared i.e. increased pulse rate, blood pressure, sweating

and movement of toes and fingers, fentanyl 0.05 mg to group A or Pentazocine 10-20 mg to group B and group C was repeated intravenously.

Adequate fluids were given in form of 5% Dextrose, Dextrose saline, Haemacoel, Lomodex, Blood as and when needed to replace blood loss and to prevent fluid defecit.

Just before the end of surgery administration of nitrous oxide was discontinued and patients were ventilated with 100% Oxygen for 2 to 3 minutes. The secretions present in mouth and pharynx were removed.

In cases where muscle relaxants were used, their residual effect was reversed, with the start of skin suturing, with 6 to 8 microgram kg^{-1} prostigmine and0.01 mg kg^{-1} of Atropine and after reversal patients were ventilated with 100% Oxygen to correct Hypoxia.

Next extubation was done and in cases of inadequate spontaneous respiration, nalorphine to group A and Doxapram to group B and group C was given.

10 mg of Nalorphine was diluted in 10 c.c. of distilled water and was given very very slowly upto a maximum of 7 mg. The effect was observed for 3 to 4 hours after injection.

Doxapram 0.5 mg kg^{-1} of body weight was diluted in 10 c.c. of distilled water and injected slowly, titrating with the adequacy of respiration, as the

respiratory effort reached to a satisfactory level further injection was stopped and patients were given 100% Oxygen to breath. These patients were observed further for 2 to 3 hours, and if the respiration again became insufficient, the dose of Doxapram was repeated.

MEASUREMENTS :

Following parameters were measured and recorded before premedication, just before induction to serve as a control, after 7 to 10 minutes of injection of Droperidol, after 3 to 5 minutes of injection of analgesic agents, during maintenance at frequent intervals in the end of anaesthesia and after Nalorphine or Doxapram if given.

1. Pulse rate and rhythm :

By palpating radial pulsations and counting for 1 minute by same observer.

2. Blood Pressure :

Blood Pressure both Systolic and Diastolic was measured to the nearest 5 mm of Hg by auscultation using the same arm and same mercury manometer. The same observer made the measurement taking care that site of auscultation was always the same.

3. Electrocardiography :

In each patients the electrocardiogram was monitored continuously on an Electrocardiograph oscilloscope (ECIL Bed Side Monitor) which was connected to a

electrocardiograph autorecorder (B.P.L.) and tracing were recorded simultaneously with other measurements using standard limb lead II.

4. Respiratory Frequency :

Counted for one minute period.

5. Respiratory Minute volume :

Minute volume was measured during one minute period using Wright's respirometer and tightly fitting mask in conscious patients and through cathetermount in anaesthetized patient.

6. Tidal Volume :

Tidal volume was measured using Wright's respirometer, five readings were taken, out of which first two were discarded and average of last three readings was recorded.

7. Complications if any in the form of apnoea, chest wall rigidity, bronchospasm, cynosis, hypotension, or hypertension and abnormal behavioural pattern were also noted and recorded.

Patients were followed for first 48 hours after surgery to record the duration of post operative analgesia, nausea, emesis, extrapyramidal symptoms and behavioural disorder and any other complication.

OBSERVATIONS

In the present study 116 cases between 12 to 65 years of age were anaesthetized with different combination of neuroleptic agents. 71 male and 45 female cases were divided in three groups.

Group A - Droperidol and Fentanyl

Group B - Droperidol and Pentazocine

Group C - Droperidol, Fentanyl and Pentazocine

Table - I

AGE AND SEX DISTRIBUTION OF CASES

Age Groups (Years)	Group A No.	%	Group B No.	%	Group C No.	%
Below 15	9	22.5	-	-	3	7.5
15 - 24	10	25.0	8	22.23	10	25.0
25 - 34	3	7.5	11	30.56	10	25.0
35 - 44	4	10.0	6	16.66	5	12.5
45 - 54	3	7.5	6	16.67	5	12.5
55 and above	11	27.5	5	13.88	7	17.5
Total	40	100	36	100	40	100
Male	23	57.5	26	72.22	22	55.0
Female	17	42.5	10	27.78	18	45.0
Total	40	100	36	100	40	100

Table - II

DISTRIBUTION OF CASES ACCORDING TO NATURE OF SURGERY

Nature of Surgery	Number of cases		
	Group A	Group B	Group C
I MAJOR ORTHOPAEDIC OPERATIONS			
a. Open reduction and internal fixation	10	7	3
b. Arthrodesis and Arthroplasty	7	2	2
c. Prosthetic replacement of head femur	2	-	3
d. Spinal surgery	-	-	3
e. Osteotomy	3	3	2
f. Saucerization, sequestrectomy and bone grafting	2	3	4
g. Surgery on nerve, tendon and skin	-	2	-
h. Amputation above knee	-	1	-
II. MAJOR GENERAL SURGERY			
a. Laparotomy	3	1	3
b. K.U.B.	3	1	2
c. Spleen	1	-	-
d. Vagotomy and Gastro-jejunostomy	-	1	1
e. Gall bladder	-	-	1
f. Hemicolectomy	-	-	1
g. Lumbar sympathectomy	-	1	-
h. Perineal surgery	1	2	2
i. Vascular surgery	-	2	-
j. Facial and oral surgery	3	1	1
k. Breast	1	1	-
III E.N.T. Radical Mastoidectomy	4	5	2
IV GYNECOLOGICAL - *Abdominal surgery	-	2	3
Perineal surgery	-	1	7
Total 116	40	36	40

*Does not include caesarean section.

Table - III (A)

FREQUENCY OF DOSES OF FENTANYL (GROUP A)

Duration of anaesthesia (minutes)	No. of cases	Fentanyl No. of doses 1*	2**	3	4	5
within 60	-	-	-	-	-	-
Within 90	10	1 (2.5%)	4 (10%)	2 (5%)	3 (7.5%)	- -
Within 120	22	1 (2.5%)	11 (27.5%)	8 (20%)	1 (2.5%)	1 (2.5%)
Within 150	7	-	1 (2.5%)	3 (7.5%)	1 (2.5%)	2 (5%)
Within 180	1	-	-	-	1 (2.5%)	-
Total	40					

Table - III (B)

FREQUENCY OF DOSES OF PENTAZOCINE (GROUP B)

Duration of anaesthesia (minutes)	No. of cases	Pentazocine No. of doses 1*	2**	3	4	5
Within 60	1	1 (2.8%)	-	-	-	-
Within 90	7	4 (11.1%)	3 (8.3%)	-	-	-
Within 120	16	10 (27.8%)	6 (16.7%)	-	-	-
Within 150	12	8 (22.2%)	4 (11.1%)	-	-	-
Total	36					

* Induction dose.
** Induction dose + one repeat dose.

Table - III (C)

FREQUENCY OF DOSES OF FENTANYL AND PENTAZOCINE (GROUP C)

Duration of anaesthesia (minutes	No. of cases	Fentanyl No. of doses 1*	2**	3	Pentazocine 1
Within 60	-	-	-	-	-
Within 90	3	2 (5%)	1 (2.5%)	-	3
Within 120	9	8 (20%)	1 (2.5%)	-	9
Within 150	27	13 (32.5%)	12 (30%)	2 (5%)	27
Within 180	1	-	1 (2.5%)	-	1
Total	40				40

* Induction dose.
** Induction dose + one repeat dose.

Table - III (D)

AVERAGE INITIAL AND REPEAT DOSE

Analgesic	DOSE RANGE (mg) Initial	Repeat
Fentanyl	0.12-0.35	0.025-0.05
Pentazocine	60-90	10-30

Table - IV

TIME TAKEN IN INDUCTION

Time in minutes	Group A	Group B	Group C
Range	10 - 20	12 - 30	10 - 25
Mean	13.25	15.20	13.90

Table - V

COURSE OF INDUCTION

Induction	Group A		Group B		Group C	
	No.	%	No.	%	No.	%
Smooth	39	97.5	31	86.0	37	92.5
Stormy	1	2.5	5	14.0	3	7.5

2.5%, 14% and 7.5% cases of group A, B and C respectively had prolong (more than 20 minutes) and stormy induction. Majority of them were males, belonging to the age group of 25 to 34 years. Five of them were alcoholic, 3 had repeated injections of Pentazocine as part of treatment prior to surgery for alleviation of pain, and one was on tranquilizer to relieve anxiety.

Table - VI (A)

CHANGES IN MEAN PULSE RATE IN GROUP A

Stages of anaesthesia	Pulse rate minute^{-1} Mean ± S.D.	Statistical significance t value	df	p value
Before pre-medication	85.92 ± 12.56	-	-	-
*Control	101.45 ± 17.88	-	-	-
Droperidol	102.50 ± 17.06	0.269	78	0.05**
Fentanyl	106.25 ± 18.16	1.129	78	0.05**
End of anaesthesia	96.72 ± 21.97	1.056	78	0.05**

* Control value taken just before induction.
** Not significant.

Table - VI (B)

CHANGES IN MEAN PULSE RATE IN GROUP B

Stages of anaesthesia	Pulse rate minute^{-1} Mean ± SD	Statistical significance t value	df	p value
Before pre-medication	88.11 ± 16.85	-	-	-
Control	109.42 ± 16.94	-	-	-
Droperidol	112.5 ± 15.00	0.817	70	0.05*
Pentazocine	110.19 ± 15.14	0.203	70	0.05*
End of anaesthesia	96.39 ± 18.75	3.091	70	0.01***

* Not significant
*** Significant

Table - VI (C)

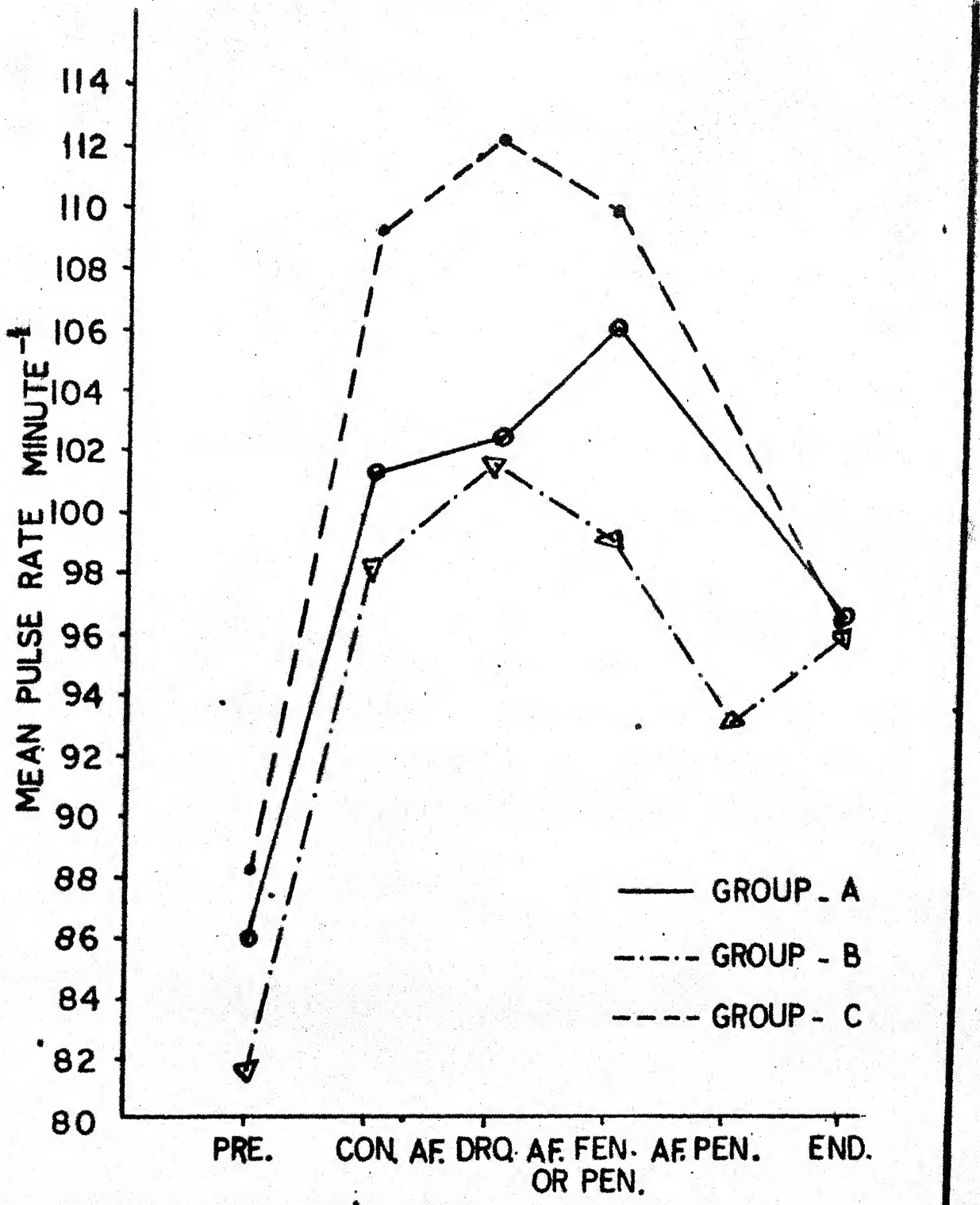
CHANGES IN MEAN PULSE RATE IN GROUP C

Stages of anaesthesia	Pulse rate minute^{-1} Mean ± SD	Statistical significance t value	df	p value
Before pre-medication	81.62 ± 24.06	-	-	-
Control	98.25 ± 16.55	-	-	-
Droperidol	101.75 ± 14.57	0.96	78	0.05*
Fentanyl	99.35 ± 16.21	0.30	78	0.05*
Pentazocine	93.30 ± 13.41	1.47	78	0.05*
End of anaesthesia	96.40 ± 14.11	0.54	78	0.05*

* Not significant

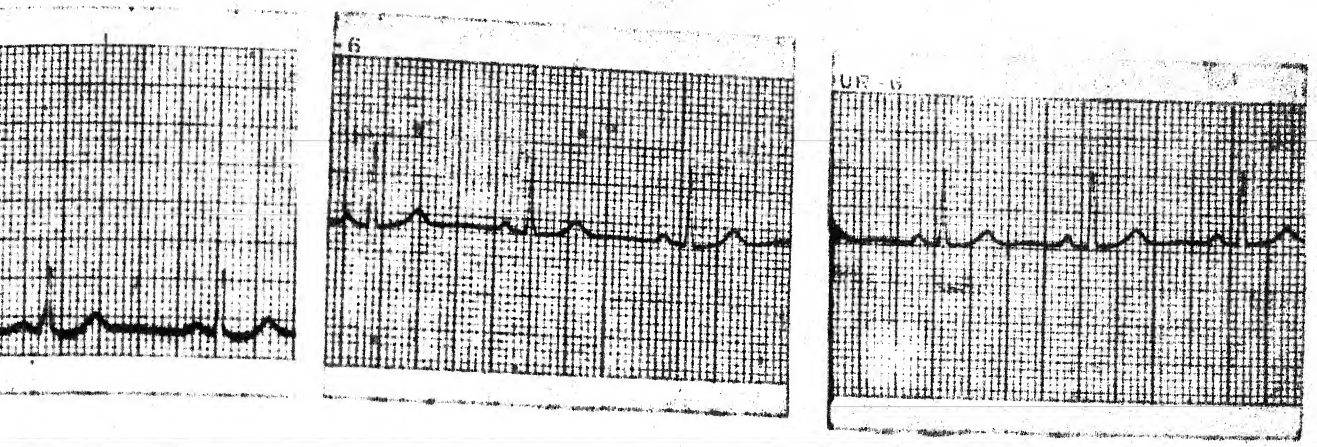
In group A, (Table VI A) atropine premedication caused marked increase in mean pulse rate to 101.45±17.88 from 85.92±12.56 (mean pulse rate before premedication). There was insignificant ($p > 0.05$) rise in mean pulse rate to 102.50±17.06 with Droperidol which was further raised with Fentanyl to 106.25±18.16 and was also statistically insignificant ($p > 0.05$). At the end of anaesthesia mean pulse rate dropped to 96.72±21.97. The difference from control was statistically insignificant.

Two patients had sinus tachycardia which started at the time of intubation and persisted till the end of surgery. Deepening the level of anaesthesia, did not control this tachycardia.

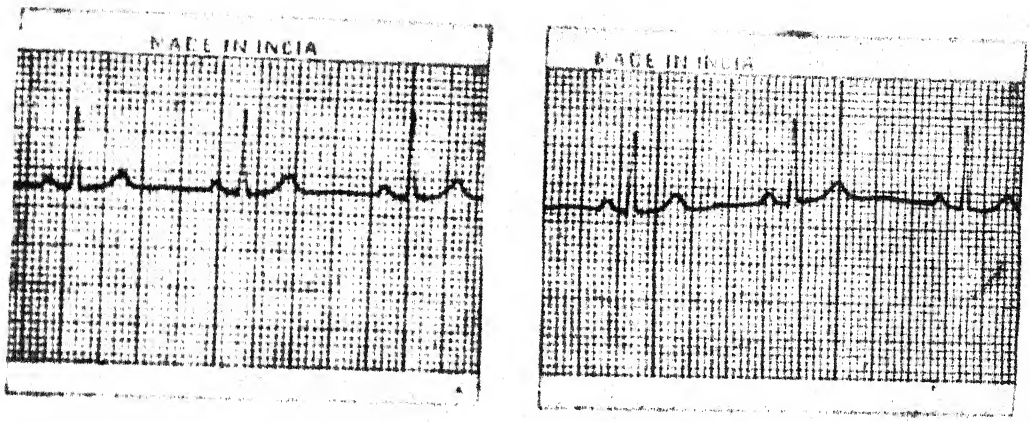


MEAN PULSE RATE DURING NLA

FIG. 6



A B C



D E

7 - E.C.G. tracings (L.II) of patient aged 46 years female undergoing Gracilis sling operation under NEUROLEPTAN-AESTHESIA.

A - Basal (Before Premedication)
E.C.G. - Normal
Rate - 68 minute^{-1}

B - Control (Just before induction)
E.C.G. - Normal
Rate - 72 minute^{-1}

C- After Droperidol
E.C.G. - Normal
Rate - 75 minute^{-1}

D - After Fentanyl
E.C.G. - Normal
Rate - 68 minute^{-1}

E - During Maintenance
E.C.G. - Normal
Rate - 68 minute^{-1}

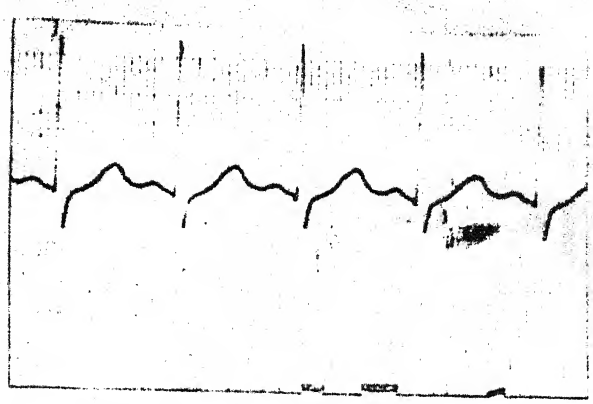
The rhythm was regular throughout the course of anaesthesia even in 3 patients who were given local infiltration of adrenaline for hemostasis.

In group B, (Table VI B) Droperidol caused rise in mean pulse rate from 109.42±42 to 112.5±15 but administration of Pentazocine caused slight fall in pulse rate, mean value being 110.19±15.14. Both these changes were insignificant statistically ($p > 0.05$). At the end of anaesthesia the mean pulse rate dropped significantly ($p < 0.01$) to 96.39±18.75.

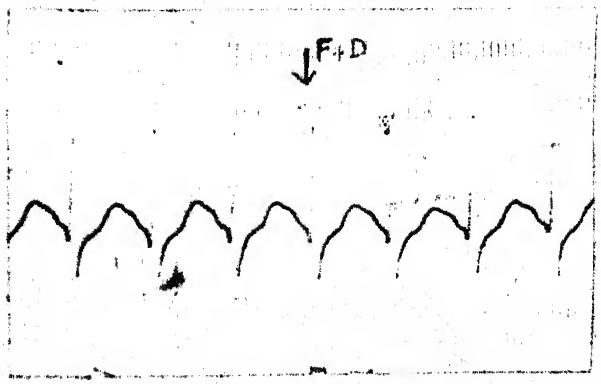
Rhythm was regular throughout the course of anaesthesia.

In group C, (Table VI C) subsequent injection of Pentazocine following Droperidol and Fentanyl caused slowing of mean pulse rate to 93.30±13.41 from the control value taken just before induction (98.25±16.55) though the difference was statistically insignificant ($p > 0.05$).

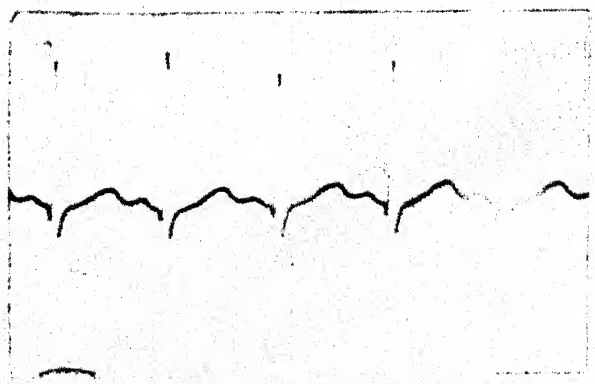
One patient had sinus tachycardia developing at the time of intubation, persisted throughout the course of anaesthesia, and did not come back to control value even after repeat dose of Fentanyl and Droperidol (Fig. No. 8). Rhythm was regular throughout the course of anaesthesia. 3 patients undergoing spinal surgery were given local adrenaline infiltration to reduce bleeding also showed no change in sinus rhythm on electrocardiography.



A- After induction with Droperidol and Fentanyl
E.C.G. - Normal
Rate - 94 minute-1
Systolic Blood Pressure - 140 mm of Hg.
Respiratory frequency - 14 minute-1



B- During maintenance
E.C.G. - Sinus tachycardia
Rate - 136 minute-1
Systolic Blood Pressure - 160 mm of Hg.
Respiratory frequency - 24 minute-1



C- Post operative (after 45 minutes)
E.C.G. - Normal
Rate - 100 minute-1
Systolic Blood Pressure - 120 mm of Hg.
Respiratory frequency - 24 minute-1

Fig. 8-E.C.G. tracings of patient aged 35 years undergoing openreduction and internal fixation under NLA showing sinus tachycardia during maintenance not responding to Fentanyl or Droperidol.

Table - VII (A)

CHANGES IN BLOOD PRESSURE IN GROUP A

Stages of anaesthesia	Systoloc blood pressure (mm of Hg) Mean ± SD	Statistical significance			Diastolic blood pressure (mm of Hg) Mean±SD	Statistical significance		
		t value	df	p value		t value	df	p value
*Control	118.75±16.96	-	-	-	75.60±10.18	-	-	-
Droperidol	114.05±14.45	1.33	78	0.05°	74.20±9.52	0.64	78	0.05°
Fentanyl	120.65±16.57	0.50	78	0.05°	74.95±8.08	0.32	78	0.05°
End of anaesthesia	120.70±13.84	0.56	78	0.05°	74.30±8.56	0.62	78	0.05°

* Just before induction.
° Not significant.

Table - VII (B)

CHANGES IN BLOOD PRESSURE IN GROUP B

Stages of anaesthesia	Systolic blood pressure (mm of Hg) Mean ± SD	Statistical significance			Diastolic blood pressure (mm of Hg) Mean ± SD	Statistical significance		
		t value	df	p value		t value	df	p value
Control	119.36±16.14	-	-	-	75.39±8.40	-	-	-
Droperidol	113.83±15.32	1.49	70	0.05°	73.39±8.60	1.00	70	0.05°
Pentazocine	121.27±16.23	0.50	70	0.05°	76.44±11.99	0.43	70	0.05°
End of anaesthesia	125.27±13.13	1.71	70	0.05°	74.94±21.71	0.16	70	0.05°

° Not significant.

Table - VII (C)

CHANGES IN BLOOD PRESSURE IN GROUP C

Stages of anaesthesia	Systolic blood pressure (mm of Hg) Mean ± SD	Statistical significance			Diastolic blood pressure (mm of Hg) Mean ± SD	Statistical significance		
		t value	df	p value		t value	df	p value
Control	118.85±29.85	-	-	-	73.75±8.07	-	-	-
Droperidol	117.35±13.97	0.19	78	0.05°	72.10±5.75	1.05	78	0.05°
Fentanyl	115.80±15.43	0.57	78	0.05°	72.05±7.78	0.96	78	0.05°
Pentazocine	122.25±13.18	0.66	78	0.05°	73.90±6.90	0.09	78	0.05°
End of anaesthesia	122.40±13.18	0.69	78	0.05°	73.65±8.94	0.50	78	0.05°

° Not significant.

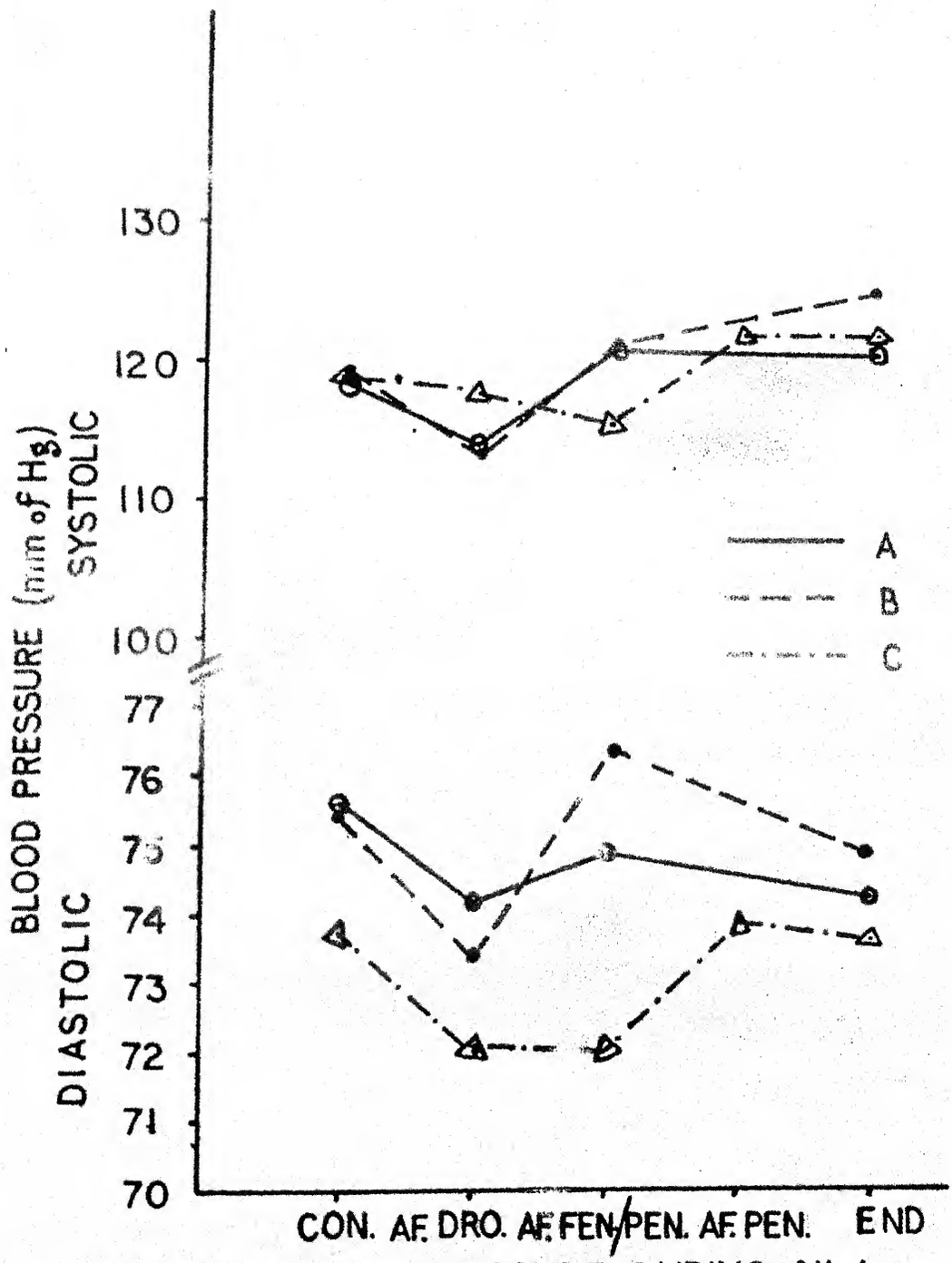
In group A, (Table VII A) changes in blood pressure both systolic and diastolic were insignificant ($p > 0.05$) after Droperidol, Fentanyl and at the end of anaesthesia. There was a fall in mean systolic blood pressure with Droperidol to 114.05±14.45 from 118.75±16.96 and fall in mean diastolic blood pressure to 74.20±9.52 from 75.60± 10.10. Subsequent injection of Fentanyl slightly raised the mean systolic and mean diastolic blood pressure to 120.65±16.57 and 74.95±8.08 respectively.

5% of patients developed systolic hypertension just after intubation which persisted upto about 60 minutes in immediate post-operative phase.

One patient undergoing spleenectomy had severe hypotension (50 mm of Hg). Peripheral circulation was well maintained. This hypotension could be corrected with rapid blood transfusion and vasopressors. Recovery from anaesthesia was as usual in this case as well.

In group B, (Table VII B), Pentazocine (60-90 mg) following Droperidol insignificantly ($p > 0.05$) raised the mean systolic blood pressure to 121.27±16.23 from 113.03±15.32 and mean diastolic blood pressure to 76.44±11.99 from 73.30±8.60. This change persisted till the end of surgery.

In group C, (Table VII C), injection of Pentazocine (10-20 mg) following Fentanyl and Droperidol also raised the mean systolic and mean diastolic blood pressure



MEAN BLOOD PRESSURE DURING NLA

FIG. 9

(115.80±15.43 to 122.25±13.18 and 72.05±7.78 to 73.90±6.90) which was statistically insignificant ($p > 0.05$).

One patient of this group had systolic hypertension just after intubation which persisted during the maintenance phase and came down to near control value at the end of anaesthesia.

Table - VIII (A)

CHANGES IN MEAN RESPIRATORY FREQUENCY IN GROUP A

Stages of anaesthesia	Respiratory frequency minute^{-1} Mean ± SD	Statistical significance		
		t value	df	p value
*Control	19.55 ± 4.53	-	-	-
Droperidol	17.92 ± 3.54	1.78	78	0.05°
Fentanyl	10.35 ± 2.81	9.89	69	0.001°°°°
End of anaesthesia	17.05 ± 4.08	2.63	78	0.05°°

*Just before induction.
°Not significant.
°°Just significant.
°°°°Highly significant.

Table ¥ VIII (B)

CHANGES IN MEAN RESPIRATORY FREQUENCY IN GROUP B

Stages of anaesthesia	Respiratory frequency minute^{-1} Mean ± SD	Statistical significance		
		t value	df	P value
Control	19.64 ± 4.04	-	-	-
Droperidol	18.11 ± 4.68	1.48	70	0.05°
Pentazocine	15.02 ± 4.30	4.71	70	0.001°°°°
End of anaesthesia	18.55 ± 3.16	1.28	70	0.05°

°Not significant.
°°°°Highly significant.

Table - VIII (C)

CHANGES IN MEAN RESPIRATORY FREQUENCY IN GROUP C

Stages of anaesthesia.	Respiratory frequency minute^{-1} Mean ± SD	Statistical significance		
		t value	df	p value
Control	18.35 ± 2.52	-	-	-
Droperidol	17.12 ± 3.07	1.94	78	0.05°
Fentanyl	11.19 ± 3.53	10.23	74	0.001°°°°
Pentazocine	16.68 ± 3.47	2.29	63	0.05°°
End of anaesthesia	17.60 ± 3.51	1.10	78	0.05°

°Not significant.
°°Just significant.
°°°°Highly significant.

Table - VIII (D)

VENTILATORY PATTERN DURING MAINTENANCE OF ANAESTHESIA

Ventilatory pattern	Group A		Group B		Group C	
	No.	%	No.	%	No.	%
Spontaneous	33	82.5	29	80.56	25	62.5
Controlled	7	17.5	7	19.44	15	37.5
Total	40		36		40	

Droperidol caused slight and insignificant fall in mean respiratory frequency ($p > 0.05$) in all the three groups.

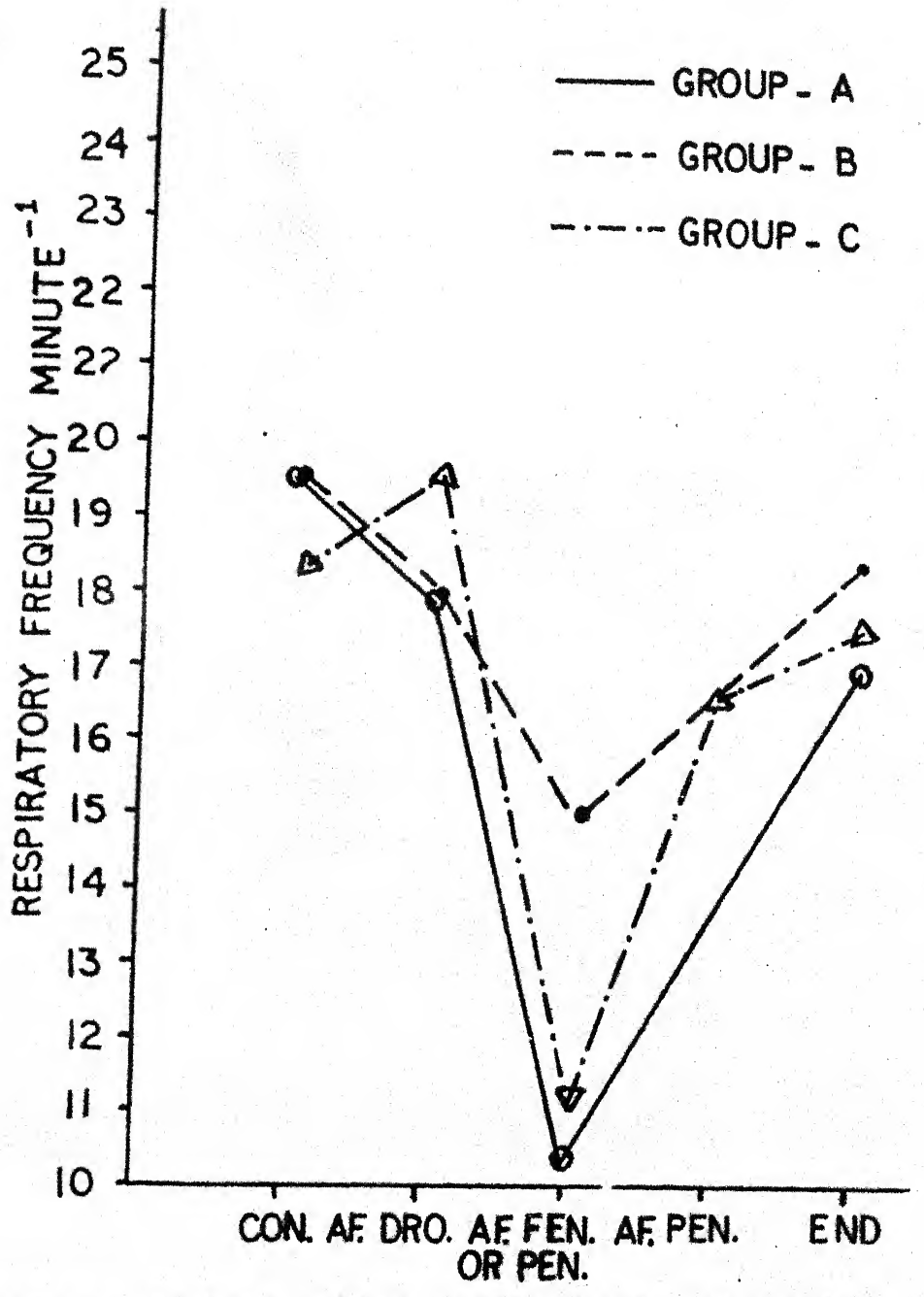
In group A, (Table VIII A), there was highly significant fall ($p < 0.001$) in respiratory frequency from 17.92±3.54 to 10.35±2.81, which returned to near control values at the end of anaesthesia.

22.5% of patients of this group (Table XII) developed apnoea 2-3 minutes after fentanyl administration, prior to intubation, but ventilation could be well maintained by assisting the respiration. Thus table VIII (A) shows mean respiratory frequency of 31 patients after Fentanyl administration.

17 patients (42.5%) had difficulty in ventilation due to chest wall rigidity, soon after Fentanyl injection which responded readily to I/V, succinylcholine.

In group B, (Table VIII B), Pentazocine following Droperidol also caused highly significant ($p < 0.001$) fall in respiratory frequency from 19.64±4.04 to 15.02± 4.30 and was less marked than that caused by Fentanyl.

In group C, (Table VIII C), the changes in respiratory frequency after Droperidol and Fentanyl were similar to group A. There was just significant fall ($p < 0.05$) in respiratory frequency from 18.35±2.52 to 16.68±3.47 after a small dose of Pentazocine. At the time of Pentazocine injection 15 patients (37.5%) were on



MEAN RESPIRATORY FREQUENCY DURING NLA.

FIG. 10

controlled ventilation (Table VIII D) and hence the table VIII C shows respiratory frequency of 25 patients after Pentazocine. 4 patients (10%) of this group developed apnoea (Table XII). 14 patients (35%) had difficulty in ventilation due to chest wall rigidity which quickly counteracted with I/V succinylcholine (Table XII).

Table - IX (A)

CHANGES IN MEAN TIDAL VOLUME AND MEAN MINUTE VOLUME IN GROUP A

Stages of anaesthesia	Tidal volume in ml Mean ± SD	Statistical significance t value	df	p value	Minute volume Litres minute^{-1} Mean ± SD	Statistical significance t value	df	p value
Control	361.75±104.44	-	-	-	6.77±1.64	-	-	-
Droperidol	319.12±95.58	1.90	78	0.05°	5.57±1.66	3.24	78	0.01°°°
Fentanyl	181.29±83.26	7.85	69	0.001°°°°	1.84±1.28	13.69	69	0.001°°°°
End of anaesthesia	313.25±105.21	2.07	78	0.05°°	5.39±2.16	3.21	78	0.01°°°

° Not significant.
°° Just significant.
°°° Significant.
°°°° Highly significant.

Table - IX (B)

CHANGES IN MEAN TIDAL VOLUME AND MEAN MINUTE VOLUME IN GROUP B

Stages of anaesthesia	Tidal volume in ml Mean ± SD	Statistical significance t value	df	p value	Minute volume Litres minute-1 Mean ± SD	Statistical significance t value	df	p value
Control	428.61±93.20	-	-	-	8.19±1.30	-	-	-
Droperidol	403.33±92.89	1.5	70	0.05°	7.09±1.58	3.23	70	0.01°°°
Pentazocine	333.61±124.10	3.67	70	0.001°°°°	4.96±2.02	8.07	70	0.001°°°°
End of anaesthesia	383.61±98.68	1.99	70	0.05°°	6.97±1.58	3.59	70	0.001°°°°

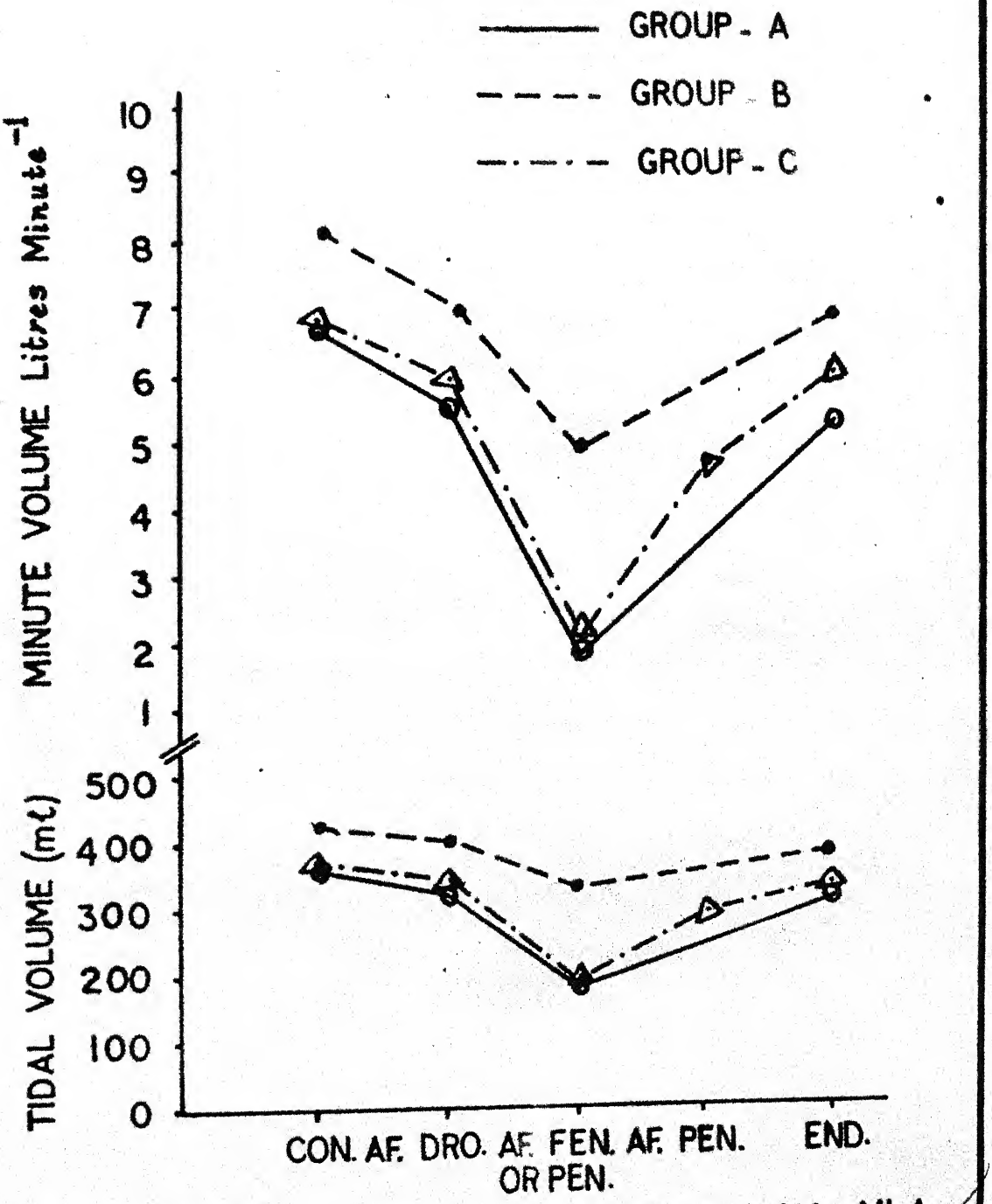
° Not significant.
°° Just significant.
°°° Significant.
°°°° Highly significant.

Table - IX (C)

CHANGES IN MEAN TIDAL VOLUME AND MEAN MINUTE VOLUME IN GROUP C

Stages of anaesthesia	Tidal volume in ml Mean ± SD	Statistical significance			Minute volume Litres minute^{-1} Mean ± SD	Statistical significance		
		t value	df	p value		t value	df	p value
Control	382.42±99.24	-	-	-	6.89±1.68	-	-	-
Droperidol	339.25±93.93	1.998	78	0.05°	6.02±1.48	2.49	78	0.05°°
Fentanyl	191.94±84.27	9.04	74	0.001°°°°	2.21±1.41	12.92	74	0.001°°°°
Pentazocine	296.00±85.15	3.73	63	0.001°°°°	4.76±2.16	4.53	63	0.001°°°°
End of anaesthesia	344.00±83.29	1.875	78	0.05°	6.09±1.98	1.95	78	0.05°

° Not significant.
°° Just significant.
°°°° Highly significant.



MEAN TIDAL & MINUTE VOLUME DURING NLA

FIG. II

Droperidol caused insignificant ($p > 0.05$) fall in mean tidal volume and significant fall ($p < 0.01$) in mean minute volume in all the three groups.

In group A, (Table IX A), there was highly significant fall ($p < 0.001$) in mean tidal volume and mean minute volume from 319.12±95.58 to 182.29±83.26 and 5.57±1.60 to 1.84±1.28 respectively, after administration of Fentanyl (31 patients). However at the end of anaesthesia both tidal volume and minute volume returned to near control value but the difference was still statistically significant ($p < 0.05$ and $p < 0.01$ respectively).

In group B, (Table IX B), Pentazocine caused further but highly significant fall ($p < 0.001$) in mean tidal volume from 403.33±92.89 to 333.61±124.70 and highly significant fall in mean minute volume from 7.09±1.58 to 4.96±2.02. However, at the end of anaesthesia both tidal volume and minute volume returned towards control value, but was still significantly ($p < 0.001$) lower.

In group C, (Table IX C), small doses of Pentazocine subsequent to Fentanyl increased the mean tidal volume and mean minute volume from 191.94±84.27 to 296.00+85.15 and from 2.21±1.41 to 4.76±2.16 respectively but these values were still significantly lower from control value ($p < 0.001$).

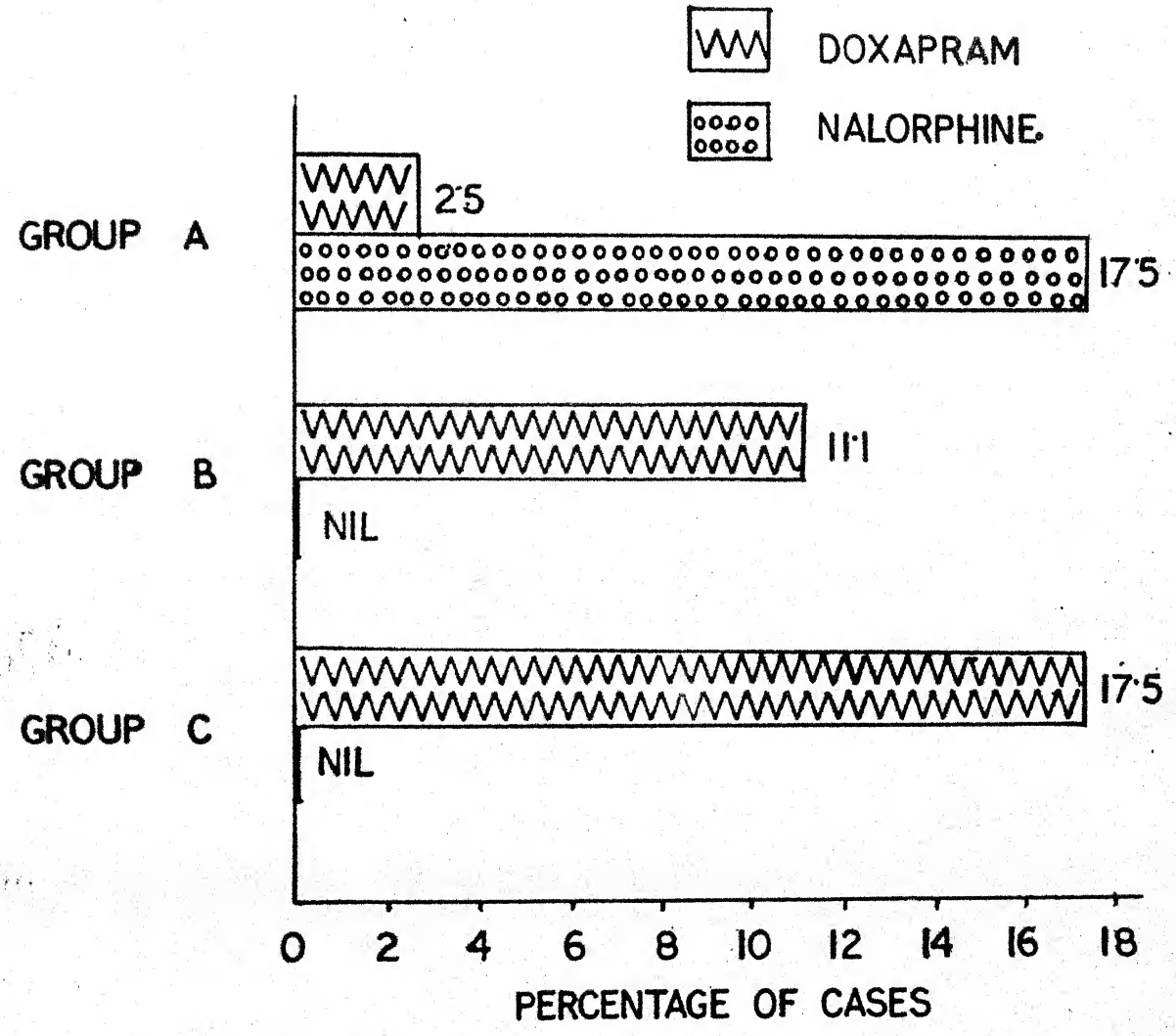

DOXAPRAM
NALORPHINE.
GROUP A
2·5
17·5
GROUP B
11·1
NIL
GROUP C
17·5
NIL
0 2 4 6 8 10 12 14 16 18
PERCENTAGE OF CASES
REQUIRING RESP. STIMULENTS

FIG. 12

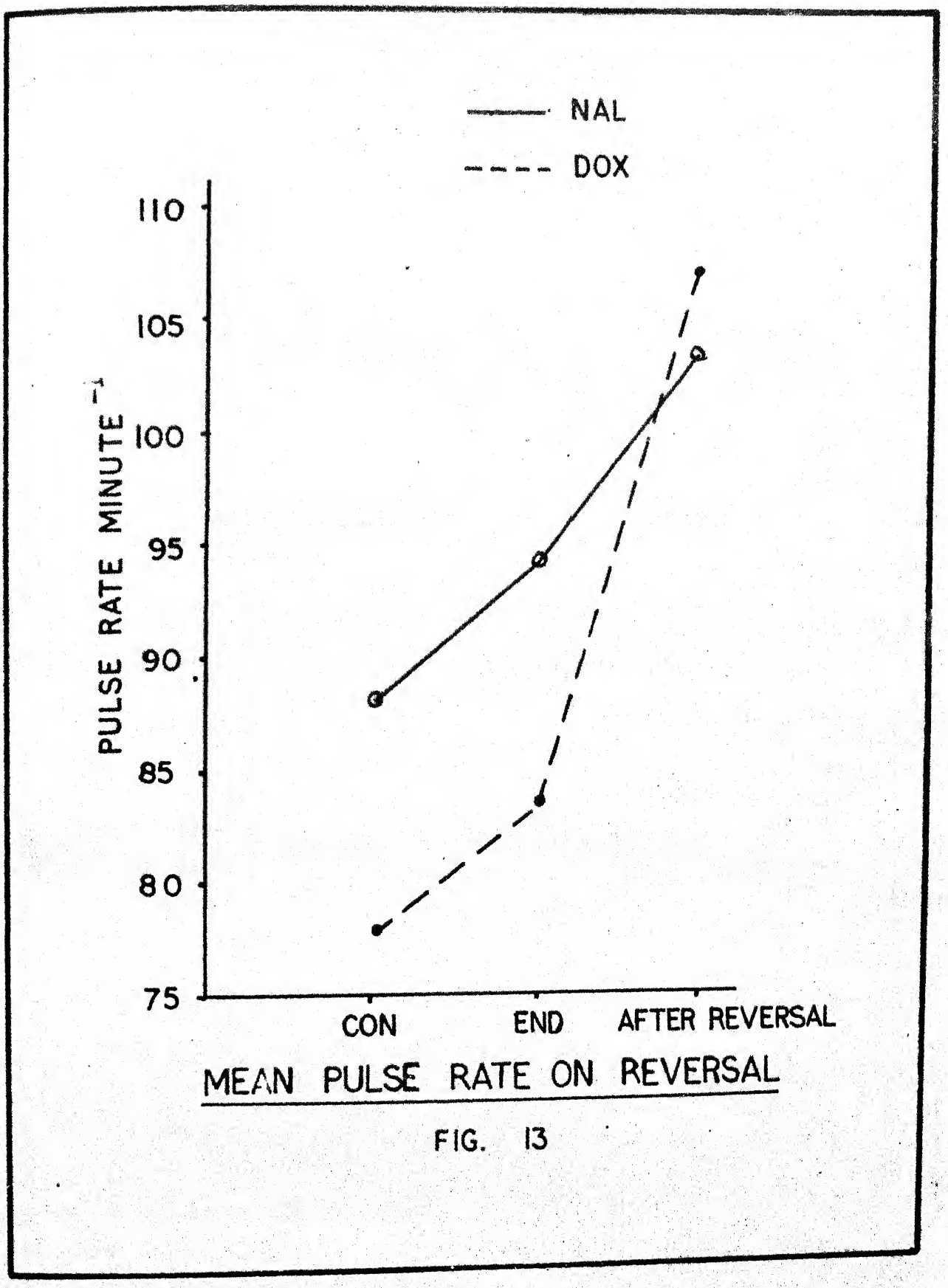

NAL
DOX
110
105
100
95
90
85
80
75
PULSE RATE MINUTE⁻¹
CON
END
AFTER REVERSAL
MEAN PULSE RATE ON REVERSAL

FIG. 13

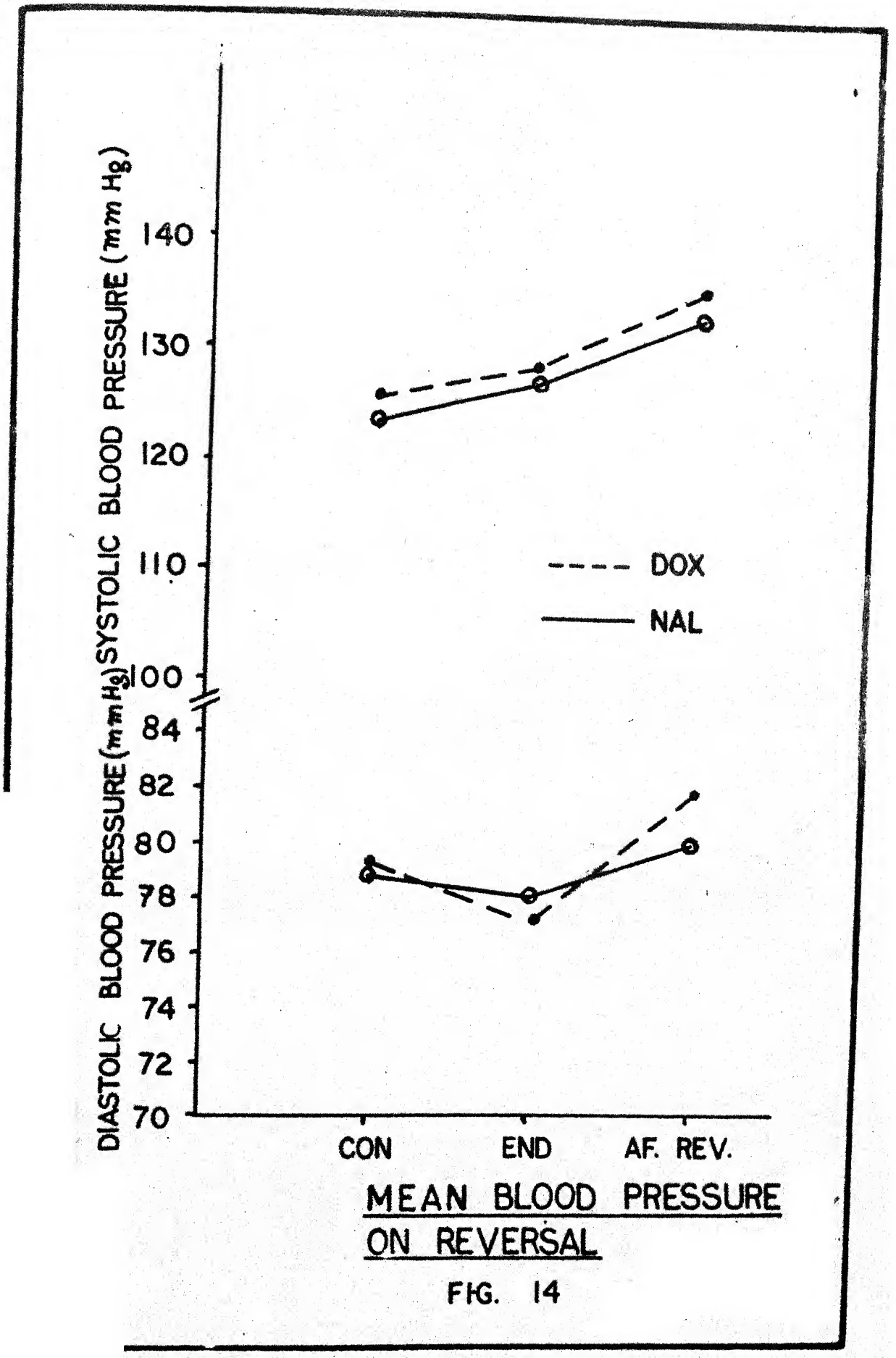
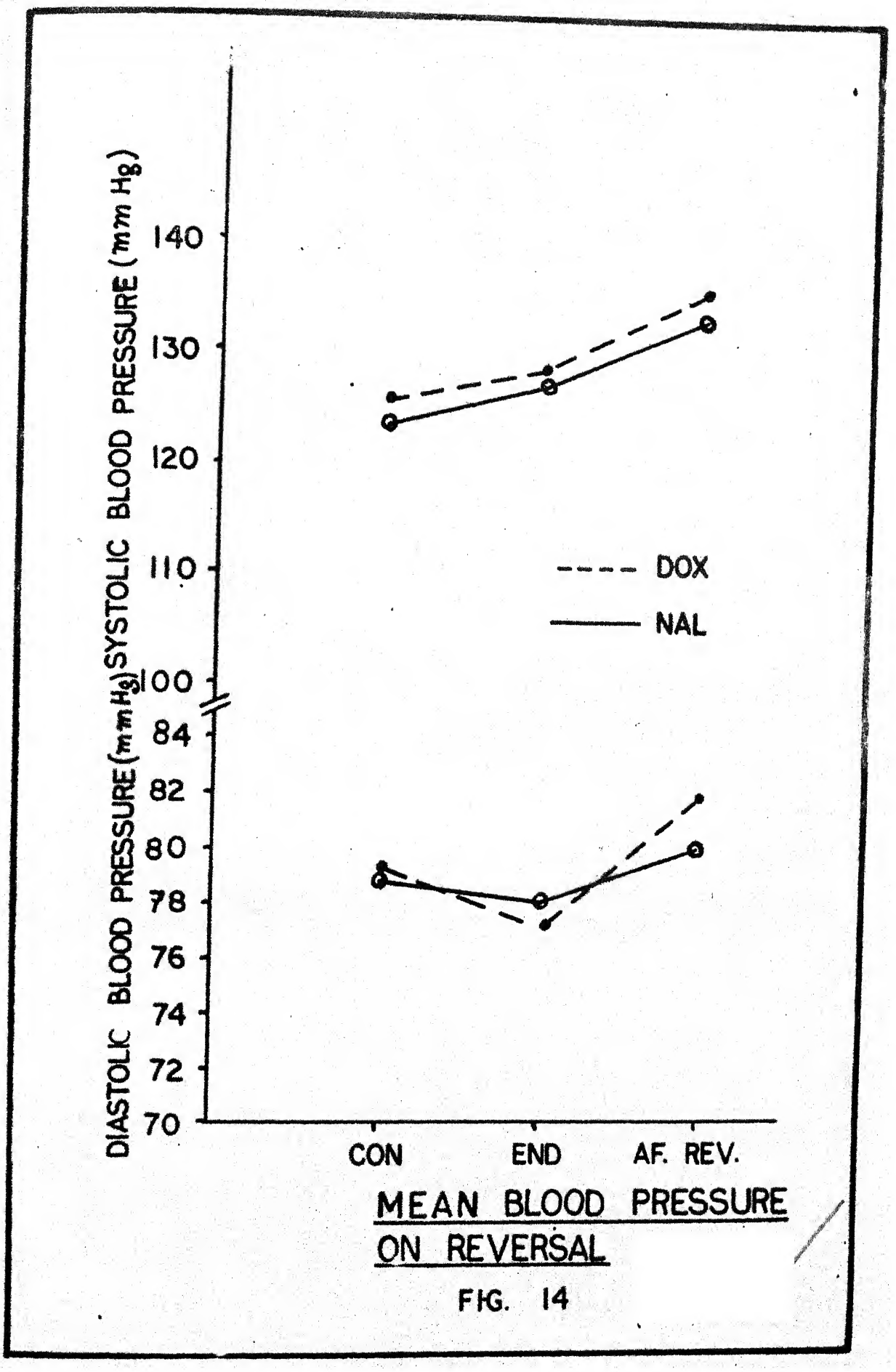

DIASTOLIC BLOOD PRESSURE (mm Hg)
SYSTOLIC BLOOD PRESSURE (mm Hg)
140
130
120
110
100
84
82
80
78
76
74
72
70
DOX
NAL
CON
END
AF. REV.
MEAN BLOOD PRESSURE
ON REVERSAL

FIG. 14



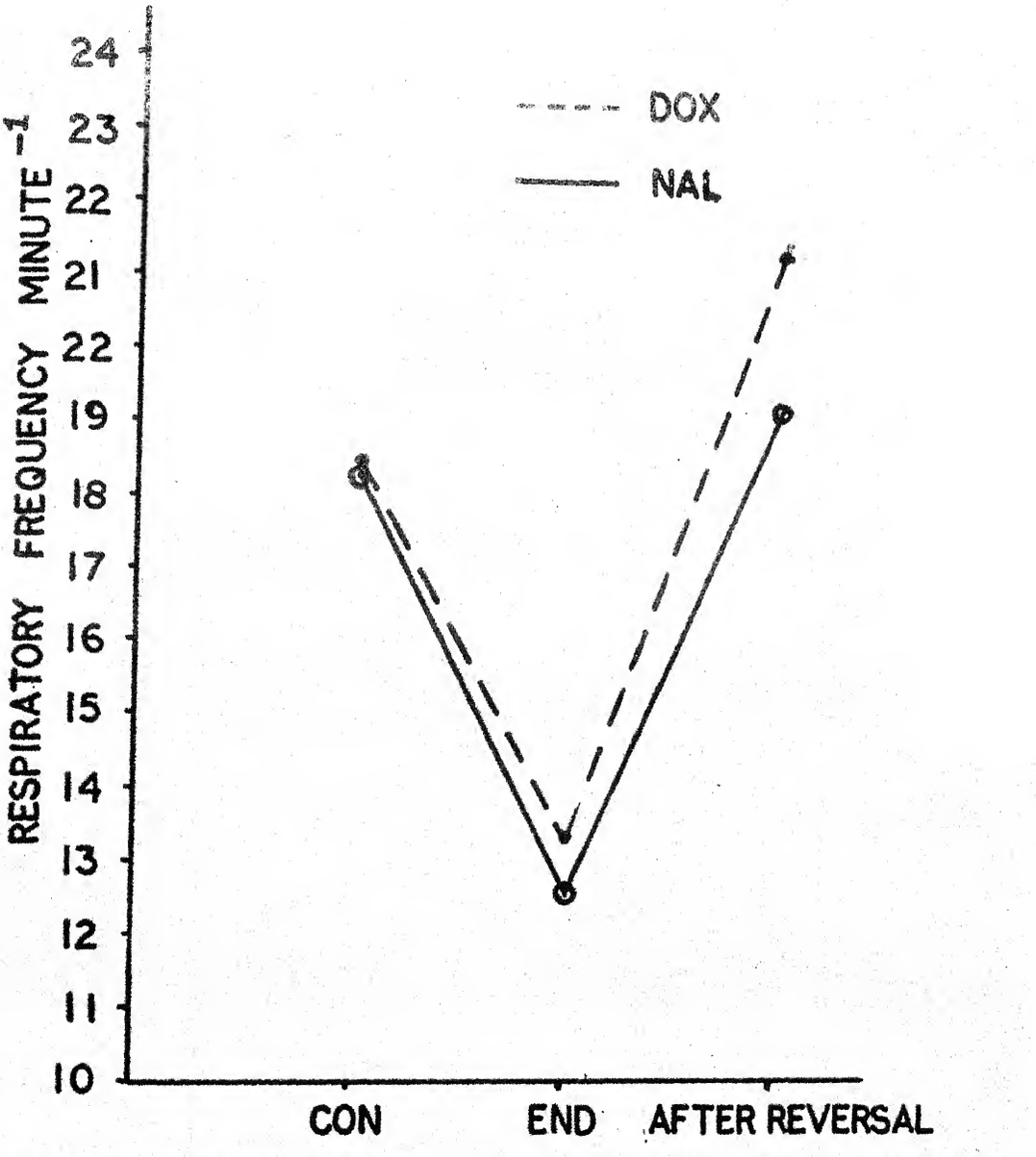
MEAN BLOOD PRESSURE ON REVERSAL

FIG. 14

Table - XI

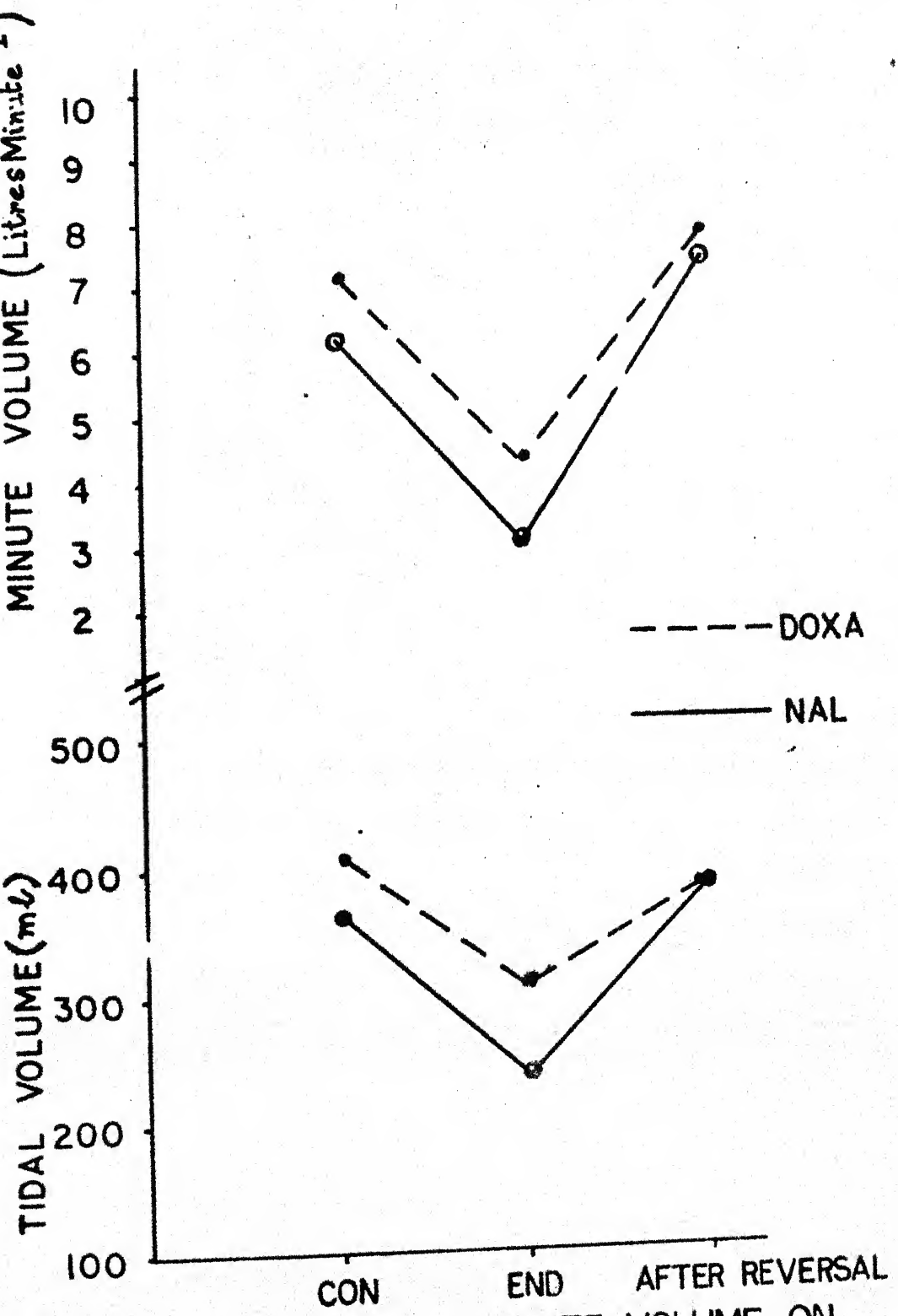
CHANGES IN CARDIORESPIRATORY PARAMETERS IN PATIENTS GIVEN RESPIRATORY STIMULANTS

Parameters	Nalorphine			Doxapram		
	Basal M±SD	After extubation M±SD	After Nalorphine M±SD	Basal M±SD	Extubation M±SD	After Nalorphine M±SD
C.V.S. changes						
Pulse rate (minute-1)	88.00±10.83	94.42±22.92	103.43±21.75	77.67±36.19	83.34±53.12	107.33±34.82
Systolic blood pressure (mm of Hg)	123.14±18.22	127.14±9.51	133.14±17.85	125.41±15.89	128.50±12.42	135.34±12.43
Diastolic blood pressure (mm of Hg)	78.86±7.56	78.00±3.46	80.00±6.43	79.50±7.14	77.17±7.31	81.83±7.16
Respiratory changes						
Respiratory frequency (minute-1)	18.29±4.96	12.57±1.90	19.14±2.79	18.50±2.28	13.33±3.11	21.33±2.33
Tidal volume (ml)	367.14±136.22	234.29±52.55	388.57±105.12	410.83±103.35	305.00±126.17	389.17±169.25
Minute volume (litres minute-1)	6.24±1.50	3.10±0.87	7.51±2.71	7.25±2.24	4.32±1.93	7.89±2.15



MEAN RESPIRATORY FREQUENCY ON REVERSAL

FIG. 15



MEAN TIDAL VOLUME & MINUTE VOLUME ON REVERSAL

FIG. 16

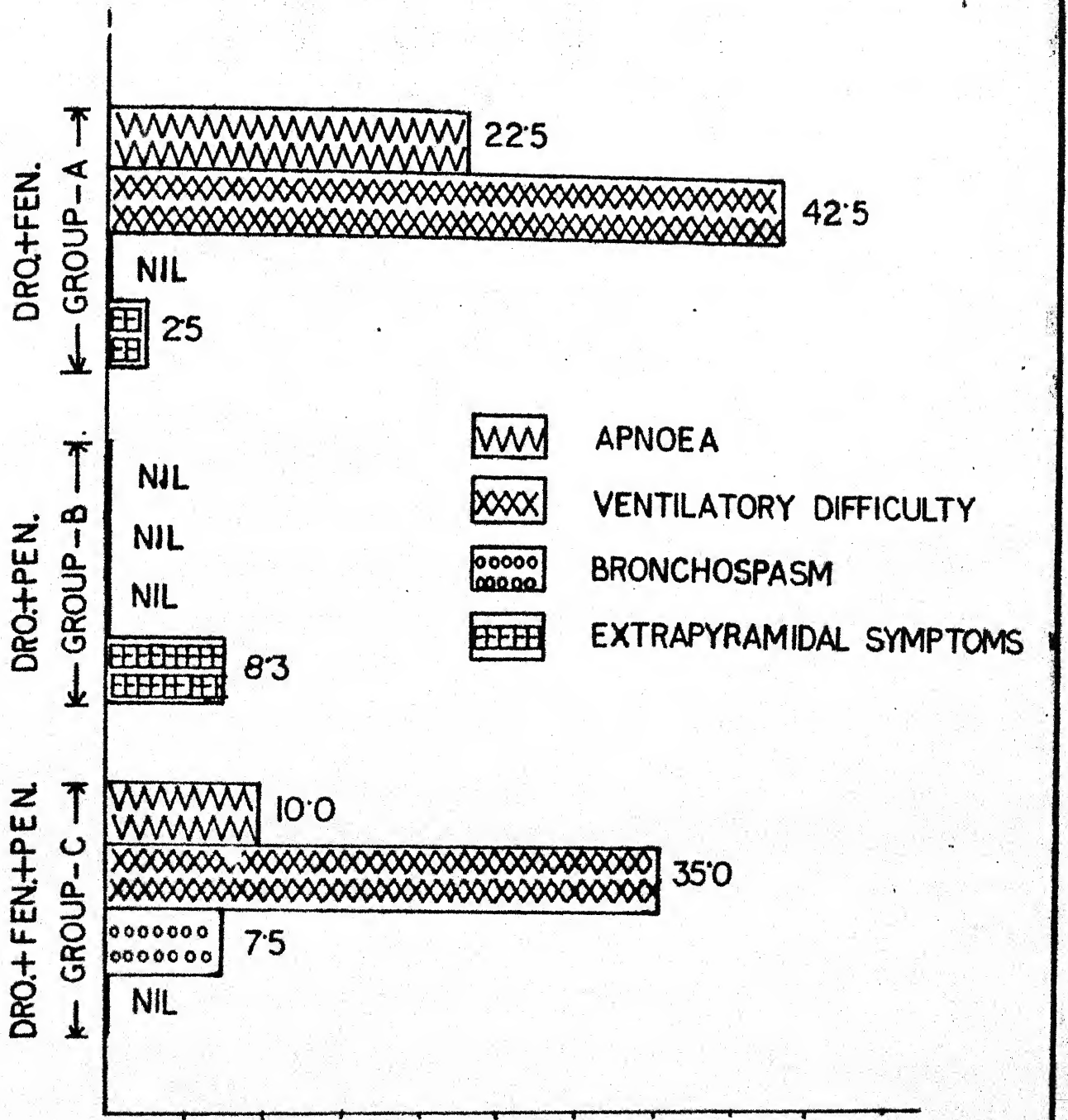
Nalorphine was given in 17.5% of cases of group A, which increased the respiratory frequency and tidal volume to 19.14±2.79 and 388.57±105.12 from the end anaesthetic value of 12.57±1.90 and 234.29±52.55 respectively. But the level of analgesia also decreased as evident from rise in pulse rate from 94.42±22.92 to 103.43±21.75 and rise in systolic blood pressure from 127.14±9.15 to 133.14±17.05.

Doxapram given in 11.1% of cases in group B and 17.5% in group C, showed effective reversal of respiratory depression as evident from rise in respiratory frequency from end anaesthetic value of 13.33±3.11 to 21.33±2.33. Increase in tidal volume and minute volume was associated with rise in pulse rate, systolic and diastolic blood pressure.

Table - XII

INCIDENCE OF OPERATIVE COMPLICATIONS

Parameters	Group A		Group B		Group C	
	No.	%	No.	%	No.	%
Apnoea	9	22.5	-	-	4	10.0
Ventilatory difficulty	17	42.5	-	-	14	35.0
Neck and face muscle rigidity	3	7.5	-	-	3	7.5
Bronchospasm	-	-	-	-	3	7.5
Hypertension	2	5.0	-	-	1	2.5
Extrapyramidal symptoms	1	2.5	3	8.3	-	-



COMPLICATIONS DURING ANAESTHESIA

FIG. 17

The problems encountered during neuroleptanaesthesia were aponea, ventilatory difficulty, facial muscle rigidity bronchospasm, hypertension, extrapyramidal symptoms and difficult induction.

Rigidity of neck and facial muscles were observed in 3 patients of group A and C, immediately after Fentanyl injection and disappeared with I/V succinylcholine.

Three cases of group C had mild degree of bronchospasm just after intubation which disappeared spontaneously within 7-10 minutes.

Extrapyramidal symptoms in the form of fine muscular twitchings of fingers and toes were noticed after induction with Droperidol. 2 patients also had fine movements of fingers and toes during intraoperative period.

Brief elevation of blood pressure was usually encountered during and after endotracheal intubation accomplished with the help of succinylcholine, but persistent rise in blood pressure was observed in two patients in group A, and one patient in group C, without any sign of inadequate analgesia.

Table - XIII

TIME TAKEN IN RECOVERY AFTER DISCONTINUATION OF NITROUS OXIDE ADMINISTRATION

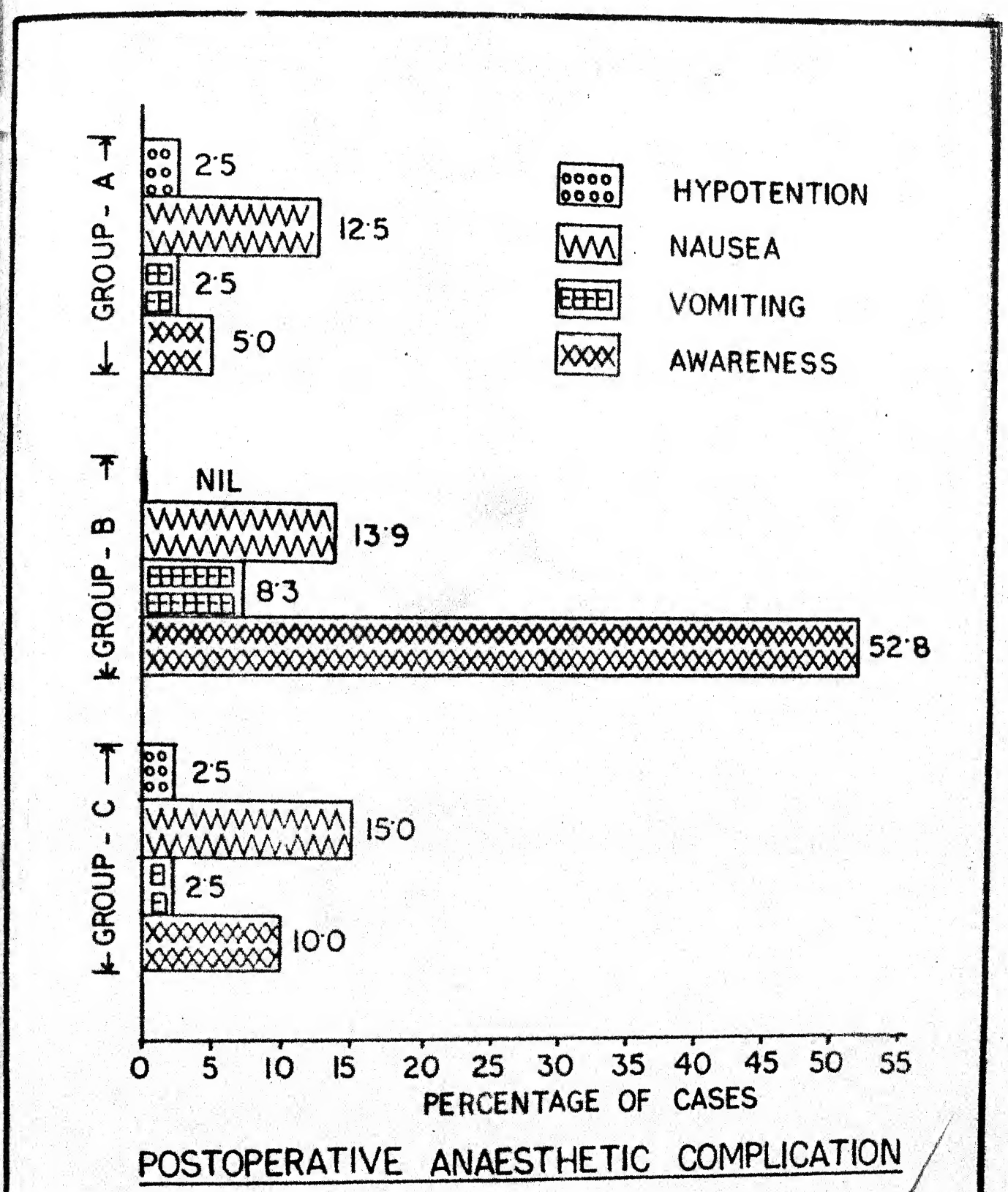
Time in minutes	Group A	Group B	Group C
Range	2 - 18	3 - 15	2 - 20
Mean	5.125	5.41	5.475

Mean recovery time after discontinuation of nitrous oxide administration was approximately the same in all the three groups. 2 patients in group A and 3 in group B had delayed recovery. At the termination of operation, patients were able to respond to simple questions and were painfree. Patients were tranquil and co-operative in recovery room, 12.1% of patients, had mental depression and were apathetic for Ist 24 hours in post-operative period.

Table - XIV

DURATION OF POSTOPERATIVE ANALGESIA

Duration (Hours)	Group A No.	%	Group B No.	%	Group C No.	%
0 - 6	27	67.5	18	50.0	3	7.5
7 - 12	7	17.5	11	30.6	11	27.5
13 - 18	3	7.5	4	11.1	13	32.5
19 - 24	3	7.5	3	8.3	13	32.5



POSTOPERATIVE ANAESTHETIC COMPLICATION

FIG. 18

Duration of post-operative analgesia was maximum in group C. 65% of patients in group C had effective analgesia upto 13-24 hours post operatively, while it was only upto 6 hours in 67.5% of cases in group A and 50% of patients in group B.

Table - XV

INCIDENCE OF POST-OPERATIVE COMPLICATIONS WITHIN Ist 24 HOURS

Parameters	Group A		Group B		Group C	
	No.	%	No.	%	No.	%
Nausea	5	12.5	5	13.9	6	15.0
Emesis	1	2.5	3	8.3	1	2.5
Awareness	2	5.0	19	52.8	4	10.0
Mental depression and apathy	3	2.5	7	19.44	4	10.0
Respiratory depression	-	-	-	-	-	-
Hypotension	1	2.5	-	-	1	2.5

DISCUSSION

The introduction of neuroleptics into clinical anaesthesia has put one of the largest feathers in the cap of anaesthesiology. It was a remarkable success achieved by the anaesthesiologist so far. It has much to boast about, as regards its utility in clinical practice. Leave aside the neurovegetative block and analgesia it produces, its popularity lies in the fact that it provides a very wide coverage of all types of patients and operations in almost all age groups, coupled with the outstanding stability of vital functions and maintenance of physiology to near normal, while nothing to say about the scope of an easy control over the level of anaesthesia.

The analysis of observations made during and after the administration of neuroleptanaesthesia to 116 patients, belonging to age group of 12-65 years, of both sexes (61.2% male and 38.8% female) undergoing major operations (Table II), induced with single dose of Droperidol and fractional doses of Fentanyl and or Pentazocine, nitrous oxide-oxygen and muscle relaxants revealed the following facts.

Induction of anaesthesia with neuroleptics was slower than the other conventional intravenous anaesthetic techniques. Mean induction time was maximum (15.2 minutes) when Droperidol and Pentazocine (Group B)

were used together with nitrous oxide - oxygen as a modified method of neuroleptanaesthesia while it was 13.25 and 13.9 minutes when Droperidol and Fentanyl were used together with nitrous oxide and oxygen in group A and C respectively. Our findings of slow induction with neuroleptanaesthesia is in conformity with Corssen and coworkers (1964), Foldes et al (1966) who observed that when 3 litres minute^{-1} nitrous oxide and 1 litre minute^{-1} oxygen mixture was administered for 6-10 minutes, after Fentanyl and Droperidol, skin incision was well tolerated.

Prolong induction time with Pentazocine could be attributed to lesser potency of Pentazocine as compared to Fentanyl. The course of induction was smooth in majority of the patients (97.5% in Group A, 86.0% in Group B and 92.5% in Group C). 13.9% incidence of prolong and stormy induction was maximum with Pentazocine (Group B), 7.5% with Fentanyl and Pentazocine (Group C) and 2.5% with Fentanyl (Group A). This observation is in accordance with the views of Holderness et al (1963), Corssen et al (1964) and Foldes et al (1970). Holderness et al (1963) were of the view that mild to moderate excitement during induction was partially related to the time of starting nitrous oxide. If inhalation was begun too early before sedation had developed, there was a greater likelihood of excitement.

Stormy induction was chiefly found in patients in the age group of 25-34 years, particularly persons indulged in alcohol and other intoxicants. Foldes et al (1970) found that these patients required increased doses of the anaesthetics and has reasoned it to be because of two factors :

1. Habituation to those drugs decreases the sensitivity of brain to all CNS depressants.
2. Both narcotics and barbiturates cause enzyme induction which results in rapid biotransformation of these agents.

To hasten the induction in these cases thiopentone sodium 100-150 mg was given intravenously. To make the patient unconscious Iwatsuki et al (1971) had suggested the use of minimal dose of thiopentone sodium or minimal concentration of halothane in this modified technique of neuroleptanaesthesia with Droperidol and Pentazocine.

Frequency of doses of analgesic drugs required was maximum (95%) in group A, out of which 72.5% of patients required 2-3 doses of Fentanyl and few of them needed upto 5 doses (Table III A). In group B 63.9% cases required single dose only, given at the time of induction of one dose only (Table III B). In group C, 55.7% patients required a single dose of both the drugs, 37.5% of patients needed repetition of Fentanyl once

only (Table III C). This frequency of doses was dependant on duration of surgery. Holderness et al (1963) have made similar observations and stated that some patients required additional doses at every 15 minutes interval, while in others, dose interval exceeded 60-75 minutes. More frequent administration of Fentanyl than Pentazocine in similar duration of surgery indicates shorter duration of action of Fentanyl than Pentazocine, similar views were also expressed by Iwatsuki et al (1971).

Cardiovascular effects :

In our study administration of Droperidol in all the three groups of cases has caused an insignificant rise in mean pulse rate ($p > 0.05$) over control values obtained before induction of anaesthesia. This confirms the views of Foldes et al (1970) and Sonntag (1973). All patients had normal sinus rhythm on electrocardiography.

Subsequent injection of Fentanyl caused insignificant change in mean pulse rate (Group A + C) and at the end of anaesthesia also it was similar to control value, the difference between the two being statistically insignificant. Similar observations were also reported by Holderness and chase (1963) and Foldes et al (1970). The rhythm remained regular throughout the course of anaesthesia in all the patients of group A and C.

Two patients in group A and one in group C developed sinus tachycardia, which started at the time of intubation

and persisted throughout the course of anaesthesia. In these cases induction was prolonged and stormy. This change in pulse rate persisted even after deepening the level of anaesthesia by further administration of Droperidol and Fentanyl. This may be probably due to stimulation of sympathetic reflexes at the time of intubation. Foldes et al (1970) encountered hypertension in some cases which was accompained by rise in pulse rate and respiratory frequency indicating inadequate analgesia, which could well be corrected by administration of analgesics. They however maintain that this could persist without any sign of inadequate analgesia which could be corrected by hypotensive drugs.

Electrocardiographic changes were insignificant even in patients who were given local adrenaline infiltration for hemostasis. This is explained on the basis of classical alpha-adrenergic blocking action of Droperidol (Janssen et al, 1963 , Schaper et al, 1963, Yelnosky et al, 1963 and Whitwam and Russell, 1971).

Subsequent injection of Pentazocine after Droperidol (group B) caused a fall, though insignificant in mean pulse rate ($p > 0.05$). At the end of anaesthesia, there was further slowing of mean pulse rate ($p < 0.01$) which was significant statistically. Slight bradycardia with the use of Pentazocine has also been reported by Potter and Payne (1970) during nitrous oxide and

halothane anaesthesia. Contrary to this Sadove et al (1964), Ahlgren and Stephen (1966) and Norris and Telfer (1968) observed rise in blood pressure accompanied by slight tachycardia in conscious patients after Pentazocine.

Droperidol caused an insignificant decrease of systolic and diastolic blood pressures ($p > 0.05$). A slight fall in blood pressure was also reported by Corssen (1964), Haase and Janssen (1965) and Foldes et al (1970), and is said to be due to fall in peripheral vascular resistance, secondary to alpha-adrenergic blockade and also to direct peripheral vaso-dilatation. There is no direct myocardial depression (Corssen, 1964).

Subsequent administration of Fentanyl in group A and C did not significantly alter the mean systolic and diastolic blood pressure ($p > 0.05$). This is in accordance with the reports of Holderness et al (1963), Dobkin et al, (1964) and Foldes et al (1970). However Fentanyl had been blamed to cause hypotension as reported by Larson (1963), Gordocki and Yelnosky (1964) and Gordotzky and Martin (1965) which last for few minutes (Brown 1965). Contradictory to this Macdonald et al (1966) and Prys-Roberts and Kelman (1967) reported insignificant rise in mean arterial pressure.

Two patients in group A and one in group C developed sustained rise in systolic blood pressure,

associated with increase in pulse rate indicating insufficient analgesia or anaesthesia, an indication for the administration of additional doses of Fentanyl. But this systolic hypertension persisted even on deepening the level of analgesia with Fentanyl or making the patient more tranquil with Droperidol. Rise in mean arterial pressure was also observed by Macdonald et al (1966) and Prys-Roberts and Kelman (1967) which they attributed to the concurrent hypercapnoea during spontaneous ventilation, rather than a direct effect of analgesic drug. In our study blood pressure and pulse rate did not come to normal values even on hyperventilating the patients, thereby ruling out the possibility of hypercarbia and/or hypoxia. The precise cause of this hyperdynamic response to neuroleptanalgesic is not fully understood. The evidences available so far are quite debatable as Giesecke et al (1967) believes that Fentanyl stimulates the release of epinephrine, as shown by increased urinary output of epine-phrine in man, while Iverson (1965) has blamed Droperidol, stating that it like other alpha-adrenergic blocking drugs decreases the tissue uptake of epinephrine and non-epinephrine.

Marked hypotension was seen only in one patient undergoing spleenectomy under classical method of neuroleptanaesthesia (Group A) who had severe blood

loss, but the peripheries remained well perfused and warm probably due to alpha-adrenergic blocking action of Droperidol. It confirms the view of Schaper et al (1963) who also reported selective blockade of alpha-receptor of the sympathetic nervous system and therefore suppressing the vasoconstrictive action of catecholamines with the use of Droperidol.

Subsequent injection of Pentazocine after Droperidol (Group B) and after Fentanyl (Group C) caused insignificant increase in systolic and diastolic blood pressure ($p > 0.05$) which persisted till the end of anaesthesia, confirming the views of Kay and coworkers (1970) and Iwatsuki et al (1971). However, Keats and Telford (1964) and Brown (1969) reported rise in blood pressure with the use of Pentazocine in doses of 2 mg/kg in conscious patient. Potter and Payne (1970) observed a significant rise in mean arterial pressure of 9.5 ± 4.9 with a dose level of 30 mg intravenously in conscious adults. Similar observations were made where Pentazocine was given during anaesthesia with nitrous oxide and halothane. The cause of this hypertensive effect, whether increased peripheral resistance or increased cardiac out put is not well established (Tammisto and colleagues, 1970) but the pallor observed after higher doses argues in favour of the former machanism. However, Kay and coworkers (1970)

did not observed any systemic hypertensive response when they used Pentazocine in conjunction with Droperidol, which they say might be due to alpha-receptor blockade produced by Droperidol.

Respiratory changes :

Droperidol caused an insignificant fall in mean respiratory frequency ($p > 0.05$) in all the three groups (Table VIII A,B and C). This is in accordance with the observation of Corssen et al (1966) and Foldes et al (1970). Although there was no significant change in mean tidal volume ($p > 0.05$), a significant fall in mean minute volume ($p < 0.05$) was registered after administration of Droperidol in all the three groups (Table IX, A,B and C). Foldes et al (1966) have also reported minimal respiratory depressant effect of Droperidol in doses of 0.10-0.15 mg kg^{-1}. This minimal fall in ventilatory efficiency due to Droperidol may be attributed to the psychomotor sedative action of the drug as has been suggested by Prys-Roberts et al (1967). However, Schaper et al (1963) and Yelnosky et al (1963) have stated "the effect of Droperidol on respiration is slight, by increasing respiratory volume relatively high doses of Droperidol, improve effective ventilation and oxygen saturation".

Subsequent administration of Fentanyl caused marked respiratory depression as evident by highly

significant fall in mean respiratory frequency, tidal volume and minute volume ($p < 0.001$ in all cases). This confirms the observations of Holderness et al (1963), Foldes et al (1966) and Corssen and coworkers (1966). In contradiction to our findings, Prys-Roberts and Kelman (1967) observed fall in respiratory frequency, minute volume and alveolar ventialtion deppite a compensatory increase in tidal volume. The lack of compensatory increase in tidal volume, in our study could be explained by the fact that the respiratory centres, under the effect of Fentanyl become insensitive to the PCo_2 levels as also suggested by Magoun (1963).

However, Jennett et al (1968) are of the opinion that there is a decrease in expiratory minute volume rather than in the frequency following administration of Fentanyl in conscious patients.

Apnoea was noted in 22.5% of cases in group A and 10% cases in group C (Table XII), 2-3 minutes after intravenous injection of Fentanyl prior to intubation. During this period patients remained conscious and responded adequately to verbal commands to breathe. Controlled respiration for a short period provided effective ventilation without loss of analgesia as also shown by Corssen et al (1966) and Prys-Roberts and Kelman (1967).

42.5% of cases in group A and 35% in group C developed ventilatory difficulty (Table XII) due to chest wall rigidity after Fentanyl administration. Holderness and coworkers (1963) also reported similar findings after rapid intravenous injection of Fentanyl. This ventilatory difficulty was readily counteracted by intravenous administration of succinylcholine thereby agreeing to the findings of Holderness et al (1963). Corssen (1966) says that "although this period does not last for more than 3-5 minutes and subsides spontaneously, it can be rapidly overcome by intravenous administration of succinylcholine".

Administration of Pentazocine following Droperidol (Group B) also caused highly significant fall in mean respiratory frequency, tidal volume and minute volume ($p < 0.001$ in all cases).

A small dose of Pentazocine subsequent to Droperidol and Fentanyl (Group C) caused just significant fall ($p < 0.05$) in respiratory frequency and highly significant fall ($p < 0.001$) in mean tidal and minute volume.

Similar observations were made by Kay and coworkers (1970) and Iwatsuki et al (1971).

The degree of ventilatory depression was more marked with Fentanyl as compared to Pentazocine. Apnoea or ventilatory rigidity was also not seen with Pentazocine which also confirms the observation made by Kay and coworkers (1970) and Iwatsuki et al (1971).

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This ventilatory depressive action of Fentanyl and Pentazocine persisted till the end of anaesthesia. But the fall in mean minute volume at the end of anaesthesia from that of control level was significant in group A ($p < 0.01$) highly significant in group B ($p < 0.001$) and insignificant in group C ($p > 0.05$).

That the significant fall in mean minute volume at the end of anaesthesia with Droperidol and Fentanyl (Group A) was also observed by Prys-Roberts and Kelman (1967) who have stated "although the ventilatory depression occurring during neuroleptanaesthesia may be prolonged into the postanaesthetic period, the blood gas tension, acid base state after neuroleptanaesthesia do not differ significantly from those found after other anaesthetic techniques".

A highly significant fall in mean minute volume persisting at the end of anaesthesia with Droperidol and Pentazocine (Group B) could be attributed to the longer duration of respiratory depressive action of Pentazocine, thereby making controllability of anaesthesia difficult, as also reported by Iwatsuki et al (1971).

An insignificant fall in mean minute volume at the termination of anaesthesia with Droperidol and Fentanyl followed by a small dose of Pentazocine could be attributed to weak narcotic antagonistic action of Pentazocine as suggested by Harris et al (1964).

Administration of Nalorphine in 17.5% cases in group A showed effective reversal of postanaesthetic respiratory depression (Table X and XI). Foldes et al (1965) Prys-Roberts and Kelman (1967) and Foldes et al (1970) have also used Nalorphine with marked successin counteracting the respiratory depression after Fentanyl.

Doxapram was tried in 11.1% of cases in group B and 17.5% in group C who were having respiratory insufficiency. The end results were found to be quite gratifying as assessed by an increase in respiratory rate and minute volume compared to the end anaesthetic values.

Yamato (1973) while studying the effect of Doxapram on ventilation after neuroleptanaesthesia observed that tidal volume and respiratory resistance increased twice as high as the level before administration by rapid single shot of 1 mg/kg of Doxapram but after 5 minutes it returned to control levels. When Doxapram 6 mg/kg was infused for 30 minutes, the minute volume stayed higher and Pa Co_2 stayed lower

than the control levels even after 60 minutes. Wakushima et al (1974) found significant increase in tidal volume after injection of Doxapram, though respiratory rate remained unchanged. The onset of effect of Doxapram was seen within 1 minute of intravenous injection and the effect lasted for about 15 minutes.

Mean recovery time (Table XII) after discontinuation of nitrous oxide administration was approximately the same being 5.12, 5.14 and 5.47 minutes in group A, B and C respectively. This compares favourably with the observations made by Iwatsuki et al (1971). In his study recovery from anaesthesia was also rapid. At the termination of operation, patients were able to respond to simple questions and were painfree, this analgesic effect lasted for a considerably longer duration, in post operative period. Patients were tranquil and co-operative in recovery room. Holderness et al (1963) also reported similar results in their study where most of the patients recovered within 15 minutes. Emergence from anaesthesia was smooth, patient awakened peaceful, free of pain and able to converse rationally. Although consciousness and orientation returned soon after discontinuance of nitrous oxide, many patients were drowsy for a number of hours thereafter, sleeping lightly, unless aroused, at which time they could converse intelligently. Holderness et al (1963),

Foldes et al (1966) and Prys-Roberts (1967) noted few patients complaining of mental depression and inability to concentrate during the remainder of the day of operation, as occured in 11.1% of cases in the present study (Table XV).

Incidence of extrapyramidal muscular twitchings and motor excitement was infrequent (Table XII) occurring at the time of induction in one patient of group A and three in group B. Corssen et al (1966) also observed extrapyramidal muscular twitchings in 5 cases in a series of 510 cases. Dobkin (1964) observed severe extrapyramidal excitation though occasional, developing in post operative period. Holderness et al (1963) reported that the transient undesirable neuromuscular reactions were common in younger age group. Patton (1975) observed that most extrapyramidal reactions caused by Droperidol are of dyskinetic type usually occurring in recovery period. He concluded that these extrapyramidal reactions tend to disappear following administration of benztropine or atropine. None of the patient in our study had extrapyramidal symptoms during post operative period, may be because of the use of single, minimal dose of Droperidol (Foldes et al, 1966).

Facial and Neck muscle rigidity was observed in 7.5% cases in both group A and C leading to difficult intubation. Tornetta in 1969 also reported acute rigidity

of facial, mandibular and pharyngeal muscles in immediate post Innovar injection period occassionally interfering with ventilation. Janis (1972) observed sustained and rapid development of acute stiffness of neck and back muscles with facial grimace, chest wall rigidity or ventilatory impairment following intravenous Innovar injection in premedication.

Awareness during anaesthesia was another drawback of this technique found in our study. The incidence of awareness was maximum in group B (52.8%) while it was 5% and 10% in group A and C respectively. This difference may be attributed to less sedative action of Pentazocine used as analgesic in group B. Presence of awareness may be attributed to insufficient intraoperative neurolepsis (Kreuscher, 1973) with use of lower doses of Droperidol (0.15 mg/kg).

In the postoperative period commonest complications were nausea, vomiting, hypotension, mental depression and apathy. None of the patients of our study had vomiting either during induction or in immediate recovery period. This could be attributed to antiemetic action of Droperidol confirming the views of Dobkin et al (1964) and Corssen et al (1964). However, nausea and vomiting occurred in Ist 24 hours during postoperative period. Vomiting occurred in 3 patients in group B and 1 patient each in group A and C. All of these

cases had undergone major intraabdominal surgery. The overall incidence of nausea and vomiting in the series of Holderness et al (1963) were 6.4% similarly Prys-Roberts and Kelman (1967) reported 4.4% incidence of nausea and vomiting with the use of Droperidol and Fentanyl. Iwatsuki et al (1971) reported 2.5% and 2.2% incidence of nausea and vomiting respectively in a series of cases who underwent surgery under modified method of neuroleptanaesthesia using Droperidol and Pentazocine.

Hypotension occurring in the postoperative period in 2.5% cases of group A and 2.5% of group C and were corrected effectively by fluid replacement. Thereby suggesting inadequate fluid replacement as the causative factor of hypotension.

None of the patients of this study had recurrent respiratory depression in postoperative period except that of in immediate recovery phase. This is because of shorter duration of action of Fentanyl, as also reported by Romagnali (1973). This shorter duration of action of Fentanyl after a single moderate dose is due to its rapid redistribution from brain to other tissues and that repeated or large doses leads to accumulation of Fentanyl and consequently ventilatory depression (Hug and Murphy, 1979).

Becker et al (1976) have reported prolong and recurrent ventilatory depression in patients who have been given Fentanyl during general anaesthesia.

Meclain and Hug (1974) suggested that Fentanyl accumulation may be associated with cumulative respiratory effects since there appears to be a close correlation between plasma level of Fentanyl and ventilatory depression in man.

CONCLUSION

After carefully analysing the observations made on 116 patients, undergoing major operations anaesthetized with classic and modified methods of neuroleptanaesthesia, following conclusions are drawn :

1. Neuroleptanaesthesia is a safe technique in patients of all age group undergoing major surgery.
2. Induction is smooth although induction time is more than the other conventional intravenous anaesthetic techniques.
3. Fentanyl though a potent analgesic has got a shorter duration of action than Pentazocine therefore frequent repeated doses of Fentanyl has to be given for surgery of longer duration not so with Pentazocine.
4. A relatively higher doses are probably required in alcoholics and patient indulged in other intoxicants for the production of smooth induction.
5. Cardiovascular stability is well maintained during surgery particularly after induction has been completed with Driperidol and Fentanyl as well as with Droperidol and Pentazocine.
6. Droperidol produces an insignificant, rise in pulse rate and fall in systolic and diastolic blood pressure.

7. Fentanyl produces an insignificant rise, in pulse rate, and systolic blood pressure, but minimal fall in diastolic blood pressure.

8. Patients with hypotensive episode during surgery due to excessive blood loss showed good peripheral perfusion due to alpha-adrenergic effect of Droperidol thereby delaying irreversibility of shock.

9. Pentazocine helps in counteracting rise in pulse rate caused by Droperidol. It also elevates the systolic and diastolic blood pressure though insignificantly.

10. Electrocardiographic tracing shows normal sinus rhythm even in cases where local adrenaline infiltration is used to obtain hemostasis.

11. Droperidol has got insignificant depressive effect on respiration.

12. Both Fentanyl and Pentazocine produces a highly significant fall in respiratory frequency, tidal volume and minute volume, though it is less marked but persist longer with Pentazocine than with Fentanyl.

13. Respiratory depression due to Fentanyl and Pentazocine remaining at the termination of anaesthesia is easily reversed by low doses of Nalorphine and Doxapram respectively.

14. Chest wall rigidity seen with Fentanyl responds well to the injection of succinylcholine chloride.

15. Pentazocine does not produce any chest wall rigidity seen frequently with Fentanyl.

16. Fentanyl is also notorious in producing apnoea which is not seen with Pentazocine.

17. Recovery from neuroleptanaesthesia is rapid, patients are able to respond to simple questions. The patients are tranquil and co-operative in the recovery room. Postoperative analgesia also stays for considerably long time.

18. Droperidol has got excellent antiemetic effect.

19. There are higher incidence of awareness during Droperidol, Pentazocine anaesthesia.

20. A small dose of Pentazocine at the end of operation reverses the respiratory depressant effects of Fentanyl while at the same time provides analgesia for much longer duration in postoperative period - a method of 'sequential anaesthesia'.

To conclude, modified method using Droperidol and Pentazocine, is better than Fentanyl group in terms of better cardiovascular stability during surgery, absence of severe respiratory depression, apnoea and ventilatory difficulty, rapid recovery from anaesthesia, longer duration of post operative analgesia. But higher incidence of awareness is a big draw back of this technique.

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In the era of mononarcosis all principal requirements of an ideal anaesthetic state i.e. analgesia, narcosis, myorelaxation and neurovegetative stability were provided by means of inhalation or intravenous anaesthetic drugs. Obtaining these several effects by means of a single volatile or injectable drug could only be possible at the risk of immediate or secondary central and peripheral toxic effects. To avoid these toxic phenomenon and to ensure the evaluation and control of each of the element in surgical anaesthesia the concept of potentialized anaesthesia was brought into light first by combining the curare with injectable barbiturates (Laborit, 1950 and Huguenard, 1950).

The term Neuroleptanalgesia was first proposed by De-Castro and Mundeleer (1959) to describe a state of indifference and immobilization termed mineralization and produced by combined administration of neuroleptic drug Haloperidol and Phenoperidine, described as NLA formula-1. Later on Janssen P.A.J. (1962) replaced Haloperidol and Phenoperidine with Droperidol and Fentanyl and described it as NLA-formula-II.

Originally neuroleptanalgesia was said to be characterized by deep sedation and analgesia without loos of consciousness. The term Neuroleptanaesthesia was proposed by Foldes et al (1966) to characterize

the unconscious state of the patient who received oxygen and nitrous oxide in addition to Droperidol and Fentanyl.

Kay and coworkers (1970) recommended Pentazocine, a non-addictive analgesic as a suitable alternative for Phenoperidine in combination with Droperidol in neuroleptanalgesia for neuroradiological procedures because of its fewer cardiovascular changes and less respiratory depression.

Inspite of highpotency and wide safety margin because of high therapeutic index, this technique has disadvantages of marked respiratory depression and ventilatory difficulty.

In the present study the technique of neuroleptanaesthesia was applied on patients undergoing major operations to evaluate the respiratory problems and depression associated with Fentanyl and cardiovascular changes due to Droperidol. The patients were premedicated with Atropine 0.3-0.65 mg, Droperidol 2.5 mg and Fentanyl 0.05 mg/Pentazocine 30 mg, 45 minutes before surgery and then the anaesthesia was induced with Droperidol 0.15-0.18 mg kg^{-1} of body weight and Fentanyl 0.003-0.004 mg kg^{-1} or Pentazocine 1.2-1.4 mg kg^{-1} with maximal utilization of nitrous oxide and oxygen. As patient became unconscious succinylcholine was given to facilitate intubation. Additional doses of

analgesic and muscle relaxants were given as and when needed. When ever possible assisted rather than controlled ventilation was used. Inadequate spontaneous respiration at the termination of anaesthesia was reversed with Nalorphine or Doxapram.

The observations viz. pulse rate and rhythm, systolic and diastolic blood pressures, respiratory frequency, tidal volume and minute volume, were measured and recorded before premedications, just before induction to serve as a control, after Droperidol, after analgesic agents, during maintenance at frequent intervals, at the end of anaesthesia and after Nalorphine or Doxapram if given.

After analysing the observations made on 116 patients belonging to age group of 12-65 years of both sexes (61.2% male and 38.8% female) undergoing major operations anaesthetized with classic and modified method of neuroleptanaesthesia, following conclusions were drawn :

1. Neuroleptanaesthesia is a safe technique in patients of all age group undergoing major surgery.
2. Induction is smooth although induction time is more than the other conventional intravenous anaesthetic techniques.
3. Fentanyl though a potent analgesic has got a shorter duration of action than Pentazocine

therefore frequent repeated doses of Fentanyl has to be given for surgery of longer duration not so with Pentazocine.

4. A relatively higher doses are probably required in alcoholics and patient indulged in other intoxicants for the production of smooth induction.

5. Cardiovascular stability is well maintained during surgery particularly after induction has been completed with Droperidol and Fentanyl as well as with Droperidol and Pentazocine.

6. Droperidol produces an insignificant, rise in pulse rate and fall in systolic and diastolic blood pressure.

7. Fentanyl produces an insignificant rise, in pulse rate, and systolic blood pressure, but minimal fall in diastolic blood pressure.

8. Patients with hypotensive episode during surgery due to excessive blood loss showed good peripheral perfusion due to alpha-adrenergic effect of Droperidol thereby delaying irreversibility of shock.

9. Pentazocine helps in counteracting rise in pulse rate caused by Droperidol. It also elevates the systolic and diastolic blood pressure though insignificantly.

10. Electrocardiographic tracing shows normal sinus rhythm even in cases where local adrenaline infiltration is used to obtain hemostasis.

11. Droperidol has got insignificant depressive effect on respiration.

12. Both Fentanyl and Pentazocine produces a highly significant fall in respiratory frequency, tidal volume and minute volume, though it is less marked but persist longer with Pentazocine than with Fentanyl.

13. Respiratory depression due to Fentanyl and Pentazocine remaining at the termination of anaesthesia is easily reversed by low doses of Nalorphine and Doxapram respectively.

14. Chest wall rigidity seen with Fentanyl responds well to the injection of succinylcholine chloride.

15. Pentazocine does not produce any chest wall rigidity seen frequently with Fentanyl.

16. Fentanyl is also notorious in producing apnoea which is not seen with Pentazocine.

17. Recovery from neuroleptanaesthesia is rapid, patients are able to respond to simple questions. The patients are tranquil and cooperative in the recovery room. Postoperative analgesia also stays for considerably long time.

18. Droperidol has got excellent antiemetic effect.

19. There are higher incidence of awareness during Droperidol, Pentazocine anaesthesia.

20. A small dose of Pentazocine at the end of operation reverses the respiratory depressant effects of Fentanyl while at the same time provides analgesia for much longer duration in postoperative period - a method of 'sequential anaesthesia'.

To conclude, modified method using Droperidol and Pentazocine, is better than Fentanyl group in terms of better cardiovascular stability during surgery, absence of severe respiratory depression, apnoea and ventilatory difficulty, rapid recovery from anaesthesia, longer duration of post operative analgesia. But higher incidence of awareness is a big draw back of this technique. The method is also convenient for clinical practice in that the analgesic used, is not a narcotic and not under D.D.A. control.